Diclofenac Topical Patch, Gel and Solution

National Drug Monograph

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VHA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action

Diclofenac is the only nonsteroidal antiinflammatory drug (NSAID) approved in the U.S. for topical application. The mechanism of diclofenac is believed to be inhibition of prostaglandin synthesis, primarily by nonselectively inhibiting cyclooxygenase. The agents covered in this review are the four diclofenac topical products approved for analgesic purposes:

- Diclofenac epolamine / hydroxyethylpyrrolidine patch (DEHP) 1.3% approved in January 2007
- Diclofenac sodium topical gel 1%, approved in October 2007
- Diclofenac sodium topical solution 1.5% with dimethyl sulfoxide (DMSO, 45.5% w/w), approved in November 2009
- Diclofenac sodium topical solution 2% with dimethyl sulfoxide (DMSO, 45.5% w/w), approved in January 2014

Indication(s) Under Review in this document (may include off label)

Also see Table 1 Product Descriptions below.

Patch 1.3%	Gel 1%	Solution 1.5% (Drops)	Solution 2% (MDP)
Topical treatment of **acute pain** due to minor strains, sprains, and contusions	Relief of the pain of **osteoarthritis** of joints amenable to topical treatment, such as the knees and those of the hands. Not evaluated for use on joints of the spine, hip, or shoulder.	Treatment of signs and symptoms of **osteoarthritis** of the knee(s)	Treatment of the pain of **osteoarthritis** of the knee(s)

MDP, Metered dose pump

Dosage Form(s) Under Review

Patch: 180 mg of diclofenac epolamine
1% gel
1.5% w/w topical solution
2% w/w topical solution

REMS

☐ REMS ☒ No REMS ☐ Postmarketing Requirements
See Other Considerations for additional REMS information

Pregnancy Rating

Patch, Solution: Category C prior to 30 weeks gestation; Category D starting at 30 weeks gestation
Gel: Category C; avoid in late pregnancy

Table 1 Diclofenac Product Descriptions

Product:	Patch 1.3% (10 cm x 14 cm)	Gel 1%	Solution 1.5% (Drops)	Solution 2% w/w (Metered Dose Pump)
Active Ingredients	180 mg diclofenac epolamine (hydroxyethylpyrrolidine) patch (1.3% or 13 mg / g adhesive)	10 mg diclofenac sodium / g of gel	16.05 mg diclofenac sodium / ml; 40 drops (~ 1.2 ml) = 19.3 mg)	20 mg diclofenac sodium / ml of solution (1 ml = 1 g of solution = 1 pump actuation)
Notable Inactive Ingredients	—	—	Dimethyl sulfoxide USP (DMSO) 45.5% w/w (penetration enhancer) Glycerin	Dimethyl sulfoxide USP (DMSO) 45.5% w/w (penetration enhancer) (Contains no glycerin)
U.S. Brand Name / Mfr(s)	FLECTOR Patch, Pfizer	VOLTAREN Gel; Endo / Novartis	PENNSAID; Nuvo Research / Mallinkrodt, licensed to Horizon Pharma	PENNSAID; Nuvo Research / Mallinkrodt, licensed to Horizon Pharma.
Generic Mfr(s)	—	Tolmar, Actavis	Apotex, Paddock, IGI Labs, Watson Labs, Taro, Lupin, Novel Labs	Paddock Labs (tentatively approved)
Non-U.S. Names	FLECTOR EP tissugel / plaster, FLECTOR patch, DIOXAFLEX, FLECTOR EP Pflaster, DICLOPLAST, DICLOREUM Tissugel, and VOTREX EP Tissugel	Diclofenac sodium 1% w/w (as diclofenac diethylamine / diethylammonium 1.16%), VOLTAREN Emulgel; VOLTAROL / CATAFLAM / VOLTAREN Gel, DIFENE gel	PENNSAID Solution 1.6% Diclofenac solution 16 mg / ml	Not marketed outside the US as of August 2015.
Notes		Diethylamine is a skin irritant and is not present in any US drug products.[1] Therefore, safety results for studies involving VOLTAREN Emulgel may not be applicable to the US VOLTAREN gel product.	The PENNSAID brand of the 1.5% solution is no longer marketed as of January 1, 2015.	More viscous than 1.5% solution. Previously referred to as PENNSAID Gel. Allows for twice daily dosing of diclofenac topical solution.

Executive Summary

Efficacy	• There is good-quality evidence that topical diclofenac products are efficacious in the treatment of localized OA of the hands or knees. • A 2012 Cochrane systematic review/ meta-analysis suggested that one cannot conclude that there are differences in the analgesic efficacy of different topical diclofenac formulations. • Based on direct evidence from individual trials, diclofenac gel and solution seem to be similar in efficacy (pain or function) to oral NSAIDs (ibuprofen 1200 mg/d, diclofenac SR 100–150 mg/d) in the treatment of patients with OA mainly of the knee. • There is a lack of direct evidence on the efficacy of the US diclofenac patch in comparison with other topical diclofenac formulations and with oral NSAIDs for acute pain due to minor musculoskeletal injuries. Indirect comparisons suggest that diclofenac gel is better than the patch.
Safety	• Based on the evidence from trials involving patients with localized OA, topical diclofenac may provide similar efficacy to oral NSAIDs with moderate improvement in safety, mainly reduction in the risk of nonserious GI adverse events. • One tradeoff with topical diclofenac is an increased risk of application site reactions, which may be intolerable for some patients and more likely with the DMSO-based solution products than the patch or gel. • The relative safety of topical diclofenac in patients with pre-existing significant risk factors for serious adverse events (e.g., history of gastrointestinal bleeding or perforation) has not been established. • Further studies are needed to assess the cardiovascular and renal risks of topical diclofenac relative to oral NSAIDs and to assess the long-term safety of topical diclofenac relative to oral NSAIDs.
Other Considerations	• DMSO-related Dry Skin. Both diclofenac solution products contain 45.5% DMSO, which can dissolve lipids on the skin surface and contribute to dry skin symptoms. • plasma concentrations of diclofenac from topically applied preparations remain much lower than those achieved with orally administered diclofenac. • Based on pooled analyses of Phase III trials, the FDA suggested that the risk of adverse events may be increased with the concomitant use of the topical solution and oral diclofenac. • Whether and to what extent the four diclofenac topical formulations can be interchangeable from the standpoints of safety, efficacy and patient acceptance are unclear.
Projected Place in Therapy	• Clinical practice guidelines recommend topical NSAIDs for OA of the hand or knee as a first-line therapy . • An important caveat to practice guideline recommendations that place topical diclofenac as an alternative first-line therapy in OA is that the currently available evidence applies mainly to short-term (≤ 12 weeks) therapy in patients who are not at high risk for NSAID-related gastrointestinal or cardiovascular harms • For patients who are at high risk for NSAID-related gastrointestinal or cardiovascular harms and require NSAID therapy following trials of alternative therapies for chronic pain due to localized osteoarthritis in a few joints, topical diclofenac gel or solution could be considered preferable to oral NSAIDs, based on their safety profile in patients with risk factors and on lower systemic exposure. However, providers should take into consideration that there have been no safety studies longer than 12 weeks in at-risk patients and no trials comparing topical diclofenac with oral NSAIDs in patients at high risk. • Topical diclofenac may be preferred over the formulary topical rubefacients because of their greater evidence of safety and efficacy. • VA Pharmacy Benefits Management prescription claims data suggest that the gel is the most commonly used topical diclofenac product and that it is used on an as-needed (p.r.n.) basis. The quantity supplied on the initial prescription of topical diclofenac may be limited to one unit (e.g., one 100-gram tube of the gel) to determine whether the product is effective and tolerated. Quantities can be adjusted to reflect patient requirements, which are most commonly one or two tubes per month. Nonpharmacologic therapies, including psychosocial therapies and cognitive behavioral therapy, are safe and effective modalities and should be used concomitantly with pharmacologic therapies for treatment of osteoarthritis.

Background

Purpose for Review

To update a previous review on diclofenac patch and add reviews of diclofenac gel and solution. To determine whether PBM **Duloxetine** for Chronic Pain Conditions Recommendations for Use referring to topical diclofenac as a Step 3 agent in OA needs to be updated.

Issues to be determined:

- ✔ Evidence of need
- ✔ Do the topical diclofenac products offer advantages over currently available VANF and nonformulary alternatives?
- ✔ Do individual topical diclofenac formulations offer advantages over the other formulations?
- ✔ What is the comparative safety of topical diclofenac versus oral NSAIDs?
- ✔ Do the topical diclofenac products have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other Therapeutic Options

Nonpharmacologic therapies for osteoarthritis include rest, physical therapy and orthoses, education on joint protection, psychosocial support such as self-management programs, diet and other weight loss measures (if appropriate), heat and cold application, hydrotherapy, and physical / occupational therapy.[2] A telephone-based self-management program that included modalities based on cognitive behavioral therapy was shown to have a small analgesic effect in Veterans with osteoarthritis,[3] although the effectiveness of self-management may depend on the particular methods used in the program.[4] Cognitive behavioral therapy has been shown to have a small to moderate analgesic effect in patients with osteoarthritis[5] and chronic noncancer pain,[6,7,8] although the benefit may be temporary.[9]

Formulary Alternatives	Other Considerations
Topical Analgesics	
Camphor 0.5% / Menthol 0.5% Lotion	There is no evidence for topical nonsalicylate rubefacients.[10]
Capsaicin Cream[11]	OTC. For minor aches and pains. For OA of the hand.[102] Can be considered first-line as adjunctive therapy or as monotherapy for mild–moderate OAK pain, according to VA/DoD guideline on nonsurgical management of OA.[12]
Menthol / Methylsalicylate Cream: • 10%–15% (Low conc) • 16%–30% (High conc)	It is noteworthy that a Cochrane systematic review / meta-analysis concluded that the available evidence does not support the use of salicylate-containing topical rubefacients for acute pain (including sprains) or chronic painful conditions (including OA).[13]
NSAIDs	
Diclofenac EC tablet Etodolac capsules, tablet Ibuprofen susp, tablet Indomethacin capsule Meloxicam tablet Naproxen tablet Sulindac tablet	Efficacious in OA and acute musculoskeletal pain (class effect)
Ketorolac injection (intra-articular)[14,15]	Preliminary evidence of potential benefit in OA
Non-acetylated Salicylates	
Salsalate	Efficacious in OA and other rheumatic disorders
Non-NSAID Analgesics	
Acetaminophen tablet, oral liquid	Recommended as first-line therapy, particularly for mild OA or pts with NSAID risk factors. However, studies show no or small analgesic effects of questionable clinical importance.[16,85]
Duloxetine	Evidence of efficacy in OAK. **Duloxetine** for Chronic Pain Conditions Recommendations for Use place duloxetine as a Step 2 formulary agent for OA. Step 2 formulary agents may be considered when primary alternatives are inadequate or poorly tolerated.
Tramadol tablet	For inadequate responders to acetaminophen, NSAIDs and duloxetine.12 Step 2 formulary alternative for OA.
Opioids, various	For patients with persistent severe osteoarthritis pain who have contraindications, inadequate response, or intolerable adverse effects with non-opioid therapies andtramadol.12

Nonformulary Alternatives	Other Considerations
Topical Analgesics	
Trolamine Salicylate	See comment under menthol / methylsalicylate cream.
NSAIDs	
Celecoxib capsule Fenoprofen tablet, capsule Flurbiprofen tablet Ketoprofen capsule, ER capsule Meclofenamate sodium capsule Mefenamic acid capsule Nabumetone tablet Oxaprozin tablet Piroxicam capsule Tolmetin tablet, capsule	Efficacious in OA and acute musculoskeletal pain (class effect)
Non-NSAID Analgesics	
Tramadol 24-h ER tablet / capsule	For inadequate response to acetaminophen, NSAIDs and duloxetine.12
Tapentadol	Step 3 nonformulary alternative for OA (see duloxetine note above).
Other Diclofenac Topicals	
Diclofenac sodium gel 3%	FDA-approved for actinic keratosis (SOLARAZE)

Efficacy

Literature Search Summary

For efficacy and effectiveness, active-controlled, randomized trials and comparative studies involving patients with the target disease states were preferred. For safety, comparative cohort studies of at least 1 year's duration were preferred. A literature search was performed on PubMed/Medline (1966 through Feb 2016) and the Cochrane Database of Controlled Trials using combinations of the search terms for the drug and formulation (*diclofenac, VOLTAREN, PENNSAID, FLECTOR, gel, solution, patch)*. Non-U.S. trade names for diclofenac patch are FLECTOR EP TISSUGEL, FLECTOR patch, DIOXAFLEX, FLECTOR EP Pflaster, DICLOPLAST, DICLOREUM Tissugel, and VOTREX EP Tissugel. Diclofenac gel is also known as diclofenac sodium 1% w/w (as diclofenac diethylamine / diethylammonium 1.16%), VOLTAREN Emulgel, and VOLTAROL / CATAFLAM / VOLTAREN Gel. An additional focused search using a combination of *topical, NSAID, hip, shoulder* and *spine* as search terms was performed on PubMed (1966 to February 2016).

Studies comparing the U.S. diclofenac topical products with non-U.S. products, studies involving healthy volunteers, studies comparing a non-U.S. topical diclofenac product with vehicle or placebo, and studies using a different salt form of diclofenac for the specific U.S. formulation (e.g., diclofenac sodium rather than epolamine patch; and diclofenac diethylammonium / VOLTAROL Emulgel 1.16% (where 11.6 mg is equivalent to 10 mg diclofenac sodium) rather than diclofenac diethylamine / VOLTAREN Emulgel 1.16%) were excluded since direct evidence using the specific product of interest was available, unless the study provided unique information (e.g., off-label use).

Search filters were English language, adults (19+ years of age), publication dates of 10 years, clinical trial, clinical trial Phase III, clinical trial Phase IV, comparative study, controlled clinical trial, meta-analysis, randomized controlled trial, review, and systematic reviews. When systematic reviews / meta-analyses of placebo-controlled trials were available, they were included in lieu of the individual placebo-controlled trials, and placebo-controlled trials published after the systematic review / meta-analyses were not sought. When foreign language reports with English abstracts were retrieved despite using the filter for English language, the studies were included if text could be translated into English and unique data were provided.

Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. Evidence was limited to published reports and FDA Medical Reviews.

Review of Efficacy

Efficacy of Topical Diclofenac in Osteoarthritis

Efficacy of Topical Diclofenac. There is good-quality evidence that topical diclofenac products are efficacious in the treatment of localized OA of the hands or knees. (See

Appendix 1: Efficacy–Safety Trials: Osteoarthritis (OA) on page 18.) In 2004, published systematic reviews showed the efficacy of topical NSAIDs in rheumatic pain using a short (2-week) assessment point, and there was no evidence of efficacy in musculoskeletal pain beyond 2 weeks.[17,18] Subsequently, larger well-designed studies of up to 12 weeks in duration[19,20] and a meta-analysis of studies lasting 4 or more weeks[21] (summarized in Table 5, page 20) supported the benefits and safety of topical diclofenac therapy beyond 4 weeks. Topical diclofenac solution and a non-US gel showed small effect sizes in reduction of pain during 4 or more weeks of therapy.

Comparison of Topical Diclofenac Products. There have been no direct comparisons among the different topical diclofenac products in the treatment of patients with OA. A 2012 Cochrane systematic review/ meta-analysis suggested that one cannot conclude that there are differences in the analgesic efficacy of different topical diclofenac formulations. NNTs (95% CI) relative to placebo for clinical success with the longest reported duration of therapy were 5.0 (3.6 to 7.8) for diclofenac patch or gel (pooled data) at 2 to 3 weeks and 10 (7.3 to 17) for diclofenac solution or gel (pooled data) at 8 to 12 weeks. (See Comparison of Different Topical Diclofenac Formulations in OA on page 21.)

Comparison of Topical and Oral Diclofenac / NSAIDs. Based on direct evidence from individual trials, diclofenac gel and solution seem to be similar in efficacy (pain or function) to oral NSAIDs (ibuprofen 1200 mg/d, diclofenac SR 100–150 mg/d) in the treatment of patients with OA mainly of the knee[22,23,49] although one study[23] showed numerically but not statistically less functional improvement with diclofenac solution 1.5% than oral diclofenac. (See Active Comparator Trials in OA on page 18.) No trials comparing diclofenac patch with oral NSAIDs were found. Results from systematic reviews / meta-analyses support that topical NSAIDs as a category are similar in efficacy to oral NSAIDs in the treatment of OA of the hands or knees. Withdrawals due to inefficacy occurred less frequently on oral than topical NSAIDs (3% versus 7%), with an NNT of 23 (95% CI 14 to 52) relative to topical NSAIDs. (See Topical Diclofenac Versus Oral NSAIDs in OA on page 20.)

Efficacy of Topical Diclofenac in Musculoskeletal Pain

Diclofenac patch is the only topical diclofenac formulation approved in the US for the treatment of patients with acute pain due to minor musculoskeletal injuries. There is a lack of direct evidence on the efficacy of the US diclofenac patch in comparison with other topical diclofenac formulations and with oral NSAIDs for acute pain due to minor musculoskeletal injuries. Indirect comparisons suggest that diclofenac gel is better than the patch.[24] (See Efficacy–Safety Trials: Musculoskeletal Pain (MSP) on page 21.)

Potential Off-Label Use

Key: DB, Double-blind; MC, Multicenter; PC, Placebo-controlled; RCT, Randomized clinical trial

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Diclofenac Epolamine Patch 1.3%

Osteoarthritis of the knee— The results of two 2-week DB PC RCTs showed efficacy of diclofenac patch for OA of the knee (N = 155 and 103).[25,26] These trials were included in a pooled analysis that showed an NNT of 3 for at least 50% pain reduction and an effect size of 0.75 (large).[27] Two small (N = 20 and 26), unpublished placebo-controlled studies add further support (Giamberardino [2005] / IBSA data on file).[114] Trials of longer duration are needed.

Localized inflammatory diseases (periarthropathies, epicondylitis / styloiditis, tendinitis / bursitis)—An active-controlled RCT (N = 190) showed that diclofenac hydroxyethylpyrrolidine (a.k.a. epolamine) 180-mg plasters was statistically superior to diclofenac diethylammonium (VOLTAREN) 1.16% Emulgel in reducing pain and pain on pressure.[28] Other supportive evidence for benefit of topical diclofenac patch in localized inflammatory diseases include placebo controlled trials in patients with periarticular pathology during rheumatic disease or inflammatory extraarticular pathology (N = 60)[29]; patients with isolated periarticular and/or tendinous pathologies (tendinitis, bursitis, epicondylitis), and inflammatory extraarticular pathologies (N = 61) (IBSA data on file)[114]; and patients with bilateral gonarthritis resistant to systemic antirheumatic treatments (abstract of DB RCT; N = 20, 40 knees).[33] One crossover study showed no statistically significant treatment effect in 80 elderly patients with tendinopathies of the shoulder and knee (abstract only).[29] A Cochrane review included 8 topical diclofenac RCTs, only one of which involved a U.S. product, diclofenac patch, for **lateral epicondylitis (tennis elbow)**.[30] This Cochrane review concluded that there was limited evidence from which firm conclusions could be drawn about the benefits or harms of topical NSAIDs for lateral epicondylitis. Very low-quality evidence suggested that topical NSAIDs may

produce a small analgesic benefit (NNTB 7; 95% CI 3 to 21) in the short-term but results were not robust in sensitivity analyses. Tolerability of topical NSAIDs was generally excellent.

Postoperative Pain—Placebo-controlled RCT results showed diclofenac patch to be superior to placebo in improving wound pain and reducing hospital stay following laparoscopic gynecologic surgery (N = 120).[31]

Thrombophlebitis, acute—Open-label study comparing diclofenac patch with usual therapy (local heparin gel / and an oral NSAID) for 10 days (with follow-up to 14 days).[114]

Venous cannulation—One placebo- and EMLA-controlled DB RCT (N = 450) showed "equal" efficacy between diclofenac patch and eutectic mixture of local anesthetic (EMLA; lidocaine / prilocaine) cream with lower incidence of skin blanching and peripheral venous thrombophlebitis with diclofenac patch than EMLA.[32] One placebo-controlled trial (N = 120) showed post-cannulation analgesic benefit with diclofenac patch.[33]

Diclofenac Sodium Gel 1%

OA of joints not evaluated in the major efficacy-safety clinical trials (e.g., spine, hip, shoulder): Several studies evaluated diclofenac gel in study populations that included subsets of patients with shoulder pain due to arthritis or tendinitis. One French-language study report (Balthazar-Letawe, 1987) evaluated in the 2012 Cochrane systematic review compared diclofenac gel (VOLTAREN EMULGEL) with indomethacin gel in 50 patients with finger or knee arthritis or **shoulder** tendinitis; however, no efficacy outcome data were useable.[52] A multicenter placebo-controlled RCT showed that diclofenac epolamine lecithin gel 1.3% (non-US product) was efficacious in 158 patients with periarthritis of the **shoulder** or lateral epicondylitis.[34] The results of an open-label observational study suggested that diclofenac epolamine gel 1.16% and piroxicam 0.5% gel were similarly effective in 173 patients with acute sprains and tendinitis of the ankle, **shoulder**, or elbow.[35] A focused literature search found no studies of diclofenac gel in patients with spine or hip pain due to OA.

***Musculoskeletal pain or acute sprains or strains of the ankles or wrists, epicondylitis of the elbow, and other soft tissue injuries*:**

- No benefit for the management of wrist extensor tenosynovitis *during* sports competition (randomized placebo-controlled trial; N = 42).[36]
- Using various primary efficacy measures, such as pain intensity and responder or "cure" rate, results of short-term (2–7 days) randomized controlled trials in patients with acute sprains or strains of the wrists or ankles due to sports or traumatic injuries have shown diclofenac gel to be
  - superior to placebo gel (N = 32)[37]
  - superior to felbinac gel (N = 384)[38]
  - superior to the following agents used as coupling media for phonophoretic application: Aquasonic 100 (N = 67)[39]; regular gel (N = 120)[40]
  - similar to the following topical NSAIDs: ketoprofen 2.5% gel (N = 1575),[41] piroxicam 0.5% gel (N = 173)[42]
  - inferior to the following topical NSAIDs: ketoprofen patch (in terms of "cure" rate; N = 223)[43]
- The following topical analgesics were shown to be noninferior to diclofenac gel: ketoprofen patch in terms of reduction in VAS pain intensity (N = 223)[43]; comfrey extract ointment (N = 164)[44]
- Diclofenac gel was shown to be similar in safety (adverse events, tolerability) to the following topical analgesics: ketoprofen 2.5% gel[41]; piroxicam gel[41,42]; comfrey extract ointment[44]

***Sunburn pain and symptoms*:** Efficacy was seen with diclofenac gel at a concentration as low as 0.1% (randomized, double-blind, vehicle-controlled trial; N = 172).[45,46]

Superficial thrombophlebitis due to intravenous infusion—An Argentinian foreign-language article with English abstract described a study comparing diclofenac topical emulsion gel with oral diclofenac and no treatment (control) in 120 patients with superficial thrombophlebitis induced by intravenous infusion ("TFSI").[47] Results for diclofenac gel (applied every 8 hours; N = 40), diclofenac oral (75 mg every 12 hours, N = 40), and control (N = 40) were as follows: average change in TFSI pain intensity from baseline, -5.70, -4.82, and –0.12 (p = 0.000); and positive response (defined as 30% or greater decrease from baseline to end of therapy at 48 hours in TFSI intensity), 60%, 60%, and 20% (p = 0.0001). Adverse events that were less common in the diclofenac gel group than in the diclofenac oral group were epigastric pain (4 vs. 17 [units not stated]; p = 0.0009) and nausea (6 vs. 16; p = 0.01). No serious adverse events were observed.

***Rheumatoid Arthritis*:** No studies found.

Diclofenac Sodium Topical Solution 1.5%

***Off-label lower dosage*—**In Canada, the recommended dosage for diclofenac 1.5% topical solution is 50 drops 3 times a day for up to 3 months.[48] This is lower than the recommended dose in the U.S. (40 drops 4 times a day).

***Temporomandibular joint dysfunction*—**One 14-day RCT (N = 36) showed no statistically significant difference between diclofenac topical solution (16 mg/ml, 10 drops 4 times a day) and oral diclofenac sodium (50 mg twice daily) in terms of pain relief. Of the 18 patients treated with oral diclofenac, 16 (88.9 %) reported epigastric pain. Transient, modest skin irritation of the temporomandibular joint region occurred in 3 (16.7%) of the 18 patients who used topical diclofenac solution.[49]

OA of joints other than the knee—A literature search found no trials evaluating diclofenac solution for OA of the shoulders, hip or spine.

Neuropathic pain—A small double-blind, crossover RCT compared diclofenac solution 1.5% (20–40 drops 3 times daily to the painful area for 2 weeks) with placebo in 28 patients with postherpetic neuralgia or complex regional pain syndrome.[50] The results showed that diclofenac solution 1.5% had small to medium benefits relative to placebo in improvement in VAS pain scores (treatment difference of 0.8; 95% CI 0.1–1.3; p = 0.04) and burning pain scores (treatment difference 1.4; 0.2–2.6; p = 0.01). There was no significant treatment difference in constant pain, hypersensitivity, shooting pain, quantitative sensory testing, or SF-36.

Diclofenac Sodium Topical Solution 2%

No studies regarding off-label use of the 2% diclofenac solution were found.

Safety

Review of Safety from Comparative Studies

Overall, the safety data from short-term clinical trials showed no increased risk of deaths or serious adverse systemic or dermal events with any topical diclofenac product.

The most common adverse events with topical diclofenac products were application site reactions, which seemed to be more common with the solution than the gel.[51]

The solution contains 45.5% DMSO, a penetration enhancing carrier which, when applied topically, has been associated with hypersensitivity / anaphylactoid reactions due to histamine release.

Safety of Topical vs. Oral NSAIDs in OA

- Three RCTs that directly compared diclofenac solution 1.5% with oral diclofenac showed lower rates of gastrointestinal adverse events,[49,22,23] and abnormal liver transaminase / ALT values,[22,23] and similar rates of cardiovascular events[22] (see Table 4 on page 18). The FDA medical review of two of these trials (the major efficacy-safety trials[22,23]) noted smaller mean decreases in hemoglobin with the topical formulation but numerically more patients had hematuria on urinalysis in the diclofenac solution group[92] (see Table 7 on page 23). The hematuria on urinalysis was considered to be a safety signal for potential renal toxicity that required further studies of longer duration. In addition, topical diclofenac solution was associated with rectal hemorrhage including bleeding hemorrhoids at a rate similar to that seen with oral diclofenac and placebo (0.1%, 0.2% and 0.3%, respectively).
- A 2010 systematic review of short-term studies (< 6 months) showed that topical diclofenac was "gastroprotective" compared with oral NSAIDs (pooled RR from 2 RCTs: 0.47; 95% CI 0.18–1.23) but there was statistically significant heterogeneity between the trials.[51] A 2012 Cochrane review showed similar findings, with oral NSAIDs more likely than topical NSAIDs to be associated with symptomatic GI adverse events (NNH 10; 7.6 to 17).[52]
- Relative to oral NSAIDs, topical diclofenac therapy also had a greater risk of application site dryness (pooled RR 12.02; 95% CI 3.96–36.54)[51] or local adverse events (NNH 6.4; 95% CI 5.3 to 8.0).[52]
- The results from indirect comparisons of the rates of withdrawals due to adverse events showed similar rates for topical and oral diclofenac in two systematic reviews.[51,52]

Safety of Topical Diclofenac in Patients with Risk Factors

- One systematic review[53] and a pooled analysis of Phase III RCTs[54] evaluated the relative safety of topical NSAIDs / diclofenac in **older individuals**.
  - According to the results of the systematic review, older adults (≥60 years) with OA mainly of the knee seemed to be more likely to develop dry skin with topical NSAIDs than oral NSAIDs, and were less likely to develop anemia, liver enzyme and renal abnormalities and "severe" gastrointestinal adverse events with topical than oral NSAIDs.[53] The rates of withdrawals due to adverse events with topical NSAIDs were similar to those with oral NSAIDs.
  - The pooled analysis showed a higher incidence of dry skin with diclofenac topical solution 1.5% and DMSO vehicle control than placebo (36.2% [$p < 0.0001$], 18.4 % [$p = 0.0142$] and 2.6%, respectively.[54] Diclofenac solution 1.5% did not increase the risks of gastrointestinal, cardiovascular and renal / urinary adverse events and withdrawals due to adverse events. Serious adverse events occurred less commonly with topical diclofenac and DMSO vehicle control than placebo (0.7%, 0.0% and 7.7%, respectively; $p \leq 0.034$).
- No increased risk of adverse events was seen in older patients (≥65 years) relative to younger patients (<65 years) in a post hoc pooled analysis of diclofenac gel study data by **age and co-morbidities** (hypertension, type II diabetes mellitus, and cerebrovascular or cardiovascular disease).[55] Gastrointestinal, cardiovascular and renal adverse events occurred at similar rates in older versus younger patients and in patients with versus without co-morbidities. Hepatic adverse events were similar in older versus younger patients. The incidence of ≥1 adverse event was similar in younger and older patients and in patients with versus without each co-morbidity except that, in patients with OA of the hand, the incidence of ≥1 adverse events was lower in patients with versus without type 2 diabetes mellitus (28.0% vs. 41.6%) and higher in patients with versus without cerebrovascular / cardiovascular disease (48.5% vs. 39.2%). Patients with OA of the knee did not show these types of co-morbidity–related disparities.
- Concomitant use of drugs known to have major or moderate interactions with diclofenac (**drug-drug interaction** group, DDI) was associated with numerically higher rates of any adverse event (62.6% versus 55.4%), headache (16.4% versus 8.4%), arthralgia (15.8% versus 8.4%) and renal adverse events (1.2% vs. 0.0%) relative to patients not taking interacting drugs (non-DDI group).[56] Cardiovascular events occurred at a numerically higher rate in the DDI group than the non-DDI group (4.7% versus 1.2%, with hypertension accounting for most cases, 2.3% versus 0.0%); however, the higher incidence of cardiovascular adverse events in the DDI group may have been related to the medical conditions for which the interacting medications were taken.
- A long-term (12-month) safety study assessing the tolerability of diclofenac sodium gel in **elderly patients and patients with risk factors** for gastrointestinal, cardiovascular or renal adverse events showed similar incidences of these adverse events between younger patients (<65 years) and older patients (≥65 years) and between patients with and patients without hypertension, type 2 diabetes mellitus, cerebrovascular / cardiovascular disease or all three co-morbidities.[57]
- Studies are needed to evaluate the risks of serious harms (e.g., gastrointestinal bleeding, cardiovascular events or renal failure) in patients with versus without risk factors and the relative safety of topical diclofenac in patients with severe or uncontrolled comorbidities including peptic ulcer disease and history of gastrointestinal bleeding / perforation.

For further details on these safety studies, see Selected Adverse Events in Older Patients and Other Patients with Risk Factors on page 24.

Relative Safety of Topical Diclofenac for Selected Adverse Events

- A 1995 record linkage case-control study in Scotland showed that there was no significant association between 45-day or ever exposure to various topical NSAIDs and **hospital admissions for upper gastrointestinal bleeding (UGIB) or perforation** after adjusting for confounding factors (i.e., concomitant oral NSAIDs and ulcer healing drugs).[58] Oral NSAIDs had a relative risk of ≥2.0 for UGIB or perforation versus community or hospital controls.
- Another case-control study in Scotland showed that topical NSAIDs are probably not associated with an independent risk for **hospitalization for acute renal failure**.[59] Oral NSAIDs, and aspirin less conclusively, were associated with an adjusted odds ratio of about 2.0 for hospitalization for acute renal failure relative to community or hospital controls. Analyses by individual topical agents could not be performed.

Further details on these studies can be found under Studies Focusing on Selected Adverse Events on page 28.

Safety Profiles from Prescribing Information

Despite the much lower systemic exposure with the three topical analgesic diclofenac products, warnings and precautions are similar to those of oral NSAIDs. For more detailed information, refer to the product prescribing information.

Topic	Patch	Gel	Solution 1.5%	Solution 2%
Boxed Warning	Cardiovascular Risk Gastrointestinal Risk	Same as for patch	Same as for patch	Same as for patch
Contraindications	• Hypersensitivity • History of asthma, urticarial, or other allergic-type reactions after taking aspirin or other NSAIDs • Use during perioperative period in the setting of CABG surgery • Use on non-intact skin	• Hypersensitivity • History of asthma, urticarial, or other allergic-type reactions after taking aspirin or other NSAIDs • Use during perioperative period in the setting of CABG surgery	• Same as for gel	• Same as for gel
Warnings / Precautions	1) Cardiovascular thrombotic events 2) Gastrointestinal effects 3) Hepatic effects 4) Hypertension 5) Congestive heart failure and edema 6) Renal effects 7) Anaphylactic reactions 8) Serious skin reactions 9) Pregnancy: Avoid use at or beyond 30 wks' gestation 10) Aspirin sensitivity and preexisting asthma 11) Accidental exposure by a child or pet 12) Avoid contact of medication with eyes and mucosa 13) Avoid concurrent use with oral NSAIDs	Same as for patch	#1–8, 10, 12, 13: Same as for patch 9) Not for use during pregnancy 14) Avoid exposure of treated knee(s) to natural or artificial sunlight	Same as for solution 1.5%
Safety Considerations	• Monitor transaminases within 4–8 wks after initiation of tx. • Hepatotoxicity may occur at any time during tx. • Use caution when patch is used concomitantly w/ potentially hepatotoxic drugs. • Caution pts to avoid taking unprescribed acetaminophen when using patch.	• See patch • Visually impaired patients may need assistance with measuring out the gel on the dosing cards.	• See patch	• See patch

Adverse Reactions

Topic	Patch	Gel	Solution 1.5%	Solution 2%
Common Adverse Reactions (Incidence ≥5%, diclofenac vs. vehicle / placebo)	Application site • Reaction (11% vs. 12%) • Pruritus (5% vs. 8%)	Application site • Reaction (7% vs. 2%)	Application site • Dry skin (32% vs. 5%) • Contact dermatitis (9% vs. 2%) Dyspepsia (8% vs. 4%) Abdominal pain (6% vs. 3%)	Application site • Dryness (22%) • Exfoliation (7%)
Common Adverse Reactions in	—	—	Rectal hemorrhage (3% vs. <1%)	See solution 1.5%

Combination with Oral Diclofenac vs. Oral Diclofenac Alone			Abnormal SCr (12% vs. 7%) Abnormal urea (20% vs. 12%) Abnormal Hg (13% vs. 9%)	
Deaths / Serious Adverse Reactions	None reported in the Clinical Studies Experience section of the prescribing information	See comment for patch	See comment for patch	See comment for patch
Most Common Adverse Reactions Leading to Discontinuation	Application site reactions (pruritus, dermatitis, burning)	Application site reactions including dermatitis	Application site reactions	Application site reactions
Notable Adverse Reaction Reports from Postmarketing Safety Surveillance (Causality not necessarily established)	Oral diclofenac hepatotoxicity	See comment for patch	See comment for patch Halitosis Ulcerative stomatitis Paresthesia Laryngismus Laryngitis Pharyngitis Skin discoloration Abnormal or blurred vision Cataract	See solution 1.5%

Drug Interactions

Interaction Type	Patch	Gel	Solution 1.5%	Solution 2%
Drug-Drug Interactions	Aspirin (generally avoid; increased adverse effects) Anticoagulants ACE Inhibitors Diuretics (monitor for renal failure) Lithium (monitor for lithium toxicity) Methotrexate (caution) Cyclosporin (caution) Oral NSAIDs (avoid unless benefits outweigh risks; monitor SCr, BUN, Hg)	See patch. Topical txs (avoid other topical products; not tested)	See gel.	See gel.

Risk Evaluation

As of 13 November 2015.

Sentinel Event Advisories	• None • Sources: ISMP, FDA, TJC

Look-alike / Sound-alike Error Potential

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Diclofenac epolamine 1.3% patch, 1% gel, 1.5% and 2% solution	Diflucan	None	None	Bromfenac Dichlorfenamide Dicloxacillin Diflucortolone Diclofenac (other topical forms – gel, cream, solution)
Flector 1.3% patch	None	None	None	Flexicort Florastor Flurbiprofen
Voltaren 1% gel	Tramadol Ultram Verelan	None	None	Voluven
Pennsaid 1.5%, 2% topical solution	None	None	None	Pemetrexed Pentasa Ansaid

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

- ***DMSO-related Dry Skin***. Both diclofenac solution products contain 45.5% DMSO, which can dissolve lipids on the skin surface and contribute to dry skin symptoms.[22,52] In the prescribing information for the topical diclofenac products, the pooled incidence of application-site dry skin was 32% with the 1.5% solution,[92] 21.5% with the 2% solution,[112] 0.4% with the gel,[1] and not reported with the patch.[116]
- ***Low Plasma Diclofenac Concentrations***. Although DMSO can increase the penetration of drug from topically applied diclofenac solution, and larger doses of topically applied diclofenac can increase systemic exposure, plasma concentrations of diclofenac from topically applied preparations remain much lower than those achieved with orally administered diclofenac. (See Appendix 5: Pharmacokinetic Considerations on page 35.) Topical diclofenac reduces the patient's systemic exposure to drug relative to oral NSAIDs.
- ***Concomitant Use of Topical and Oral NSAIDs***. Concurrent use of diclofenac solution 1.5% and an oral NSAID showed no additional analgesic or selected systemic adverse events over oral NSAIDs alone in the primary study.[22] Based on pooled analyses of Phase III trials, the FDA suggested that the risk of adverse events may be increased with the concomitant use of the topical solution and oral diclofenac.[92] (See Table 7, page 23.) The low number of cases precluded an adequate assessment. No other topical diclofenac products have been studied in combination therapy with the oral formulation.
- ***Interchangeability of Topical Products***. Whether and to what extent the four diclofenac topical formulations can be interchangeable from the standpoints of safety, efficacy and patient acceptance are unclear; they may result in different levels of effects because of differences in their systemic bioavailability, which may vary among patients depending on the amount of product applied.
- ***Extensive Actual Experience.*** Topical NSAIDs have been marketed outside the US for more than a decade (UK approval was in 1996 for ibuprofen gel 5% and 1997 for diclofenac gel). Topical diclofenac patches and gel (1.16% and 2.32%) are available over-the-counter in the UK.
- ***Risk of Hepatotoxicity for Oral Diclofenac.*** Oral diclofenac is associated with the highest risk of hepatotoxicity among the oral NSAIDs.

Dosing and Administration

The total daily dosage of diclofenac salt varies by product, ranging from about 80 mg / d of diclofenac sodium with the 1.5% and 2% topical solutions to 360 mg of diclofenac epolamine with the patch (Table 2). Diclofenac epolamine 180 mg is equivalent to 129.7 mg of diclofenac acid, which corresponds to diclofenac sodium 140 mg.[60] Both the gel and 1.5% solution / drops are applied 4 times a day whereas the patch and 2% w/w solution in a metered dose pump are applied twice a day (Table 2). Although the daily dose of diclofenac epolamine is the highest of the three products, the patch has been shown to release only 9 mg of drug and seems to produce the lowest systemic exposure of the three products (Table 20, page 35).

Table 2 FDA-approved Dosing Recommendations for Topical Diclofenac Formulations

	Patch 1.3% (180 mg diclofenac epolamine / patch)	Gel 1% (10 mg diclofenac sodium / gram of gel	Solution 1.5% (Drops) (16.05 mg diclofenac sodium / ml; 40 drops (~ 1.2 ml) = 19.26 mg)	Solution 2% (Metered Dose Pump) (20 mg diclofenac sodium / g of solution; 20 mg / pump actuation)
Dosage	1 patch to the most painful area twice a day	Lower Extremities (foot, knee, ankle): 4 g to affected area 4 times daily (max. 16 g/d per any single joint) Upper Extremities (hand, elbow, wrist): 2 g to affected area 4 times daily (max. 8 g/d per any single joint)	40 drops per knee 4 times a day	40 mg (2 pump actuations) per knee 2 times a day
Maximum Dose	Not stated. One patch per dose was the maximum dose given in clinical trials.	32 g / d for all affected joints	Amounts greater or less than the recommended dose have not been studied and are not recommended.	Amounts greater or less than the recommended dose have not been studied and are not recommended.
Administration		One dosing card (supplied in product carton) should be used for each application.	Apply to clean, dry skin. Dispense 10 drops at a time either directly onto the knee or first into the hand and then onto the knee. Spread solution evenly around front, back and sides of the knee. Repeat this procedure until 40 drops have been applied and the knee is completely covered with solution.	Apply to clean, dry skin. The pump must be primed before first use by fully depressing the pump mechanism (actuation) 4 times while holding the bottle in an upright position. This portion should be discarded to ensure proper priming of the pump. No further priming of the bottle should be required. Dispense solution into the hand and then apply evenly around front, back, and sides of the knee.
Special Precautions / Other Instructions	• Do not apply to damaged or non-intact skin. • Do not wear patch when bathing or showering. • If adhesion is a problem, the edges of the patch may be taped down or patients may overlay the patch with a breathable, nonocclusive mesh netting sleeve (such as CURAD Hold Tite or SURGILAST Tubular Elastic Dressing) where appropriate (e.g., ankles, knees or elbows). • Wash hands after applying, handling or removing the patch. • Avoid contact of medication with eyes.	• Do not apply gel to open wounds. • Avoid showering/bathing for at least1 hour after application. • Wash hands after use, unless the hands are the treated joint. If gel is applied to the hand(s) for treatment, patient should not wash the treated hand(s) for at least 1 hour after the application. • Avoid contact of gel with eyes and mucous membranes. • Do not apply external heat and/or occlusive dressings to treated joints. • Avoid exposure of the treated joint(s) to sunlight. • Do not use gel concomitantly with sunscreens, cosmetics, lotions, moisturizers, insect repellants, or other topical medications on the same skin sites (concomitant use with these products has not been evaluated). • Concomitant use of gel with oral NSAIDs has not been evaluated, and may increase adverse NSAID effects.	• Avoid showering / bathing for at least 30 min after application. • Wash and dry hands after use. • Do not apply solution to open wounds. • Avoid contact of solution with eyes and mucous membranes. • Do not apply external heat and/or occlusive dressings to treated knees. • Avoid wearing clothing over treated knee(s) until the knee is dry. • Protect treated knee(s) from sunlight; do not use sunlamps and tanning beds. • Wait until the treated area is dry before applying sunscreen, insect repellent, cosmetics, topical medications or other topical medication. • Until the treated knee(s) are completely dry, avoid skin-to-skin contact between other people and the treated knee(s).	• Avoid showering/bathing for at least 30 minutes after the application. • Wash and dry hands after use. • Do not apply to open wounds. • Avoid contact of solution with eyes and mucous membranes. • Avoid wearing clothing over the product-treated knee(s) until the treated knee is dry. • Protect the treated knee(s) from natural and artificial sunlight. • Concurrent use of product under the conditions of heat application, occlusive dressings overlay, or exercise is not recommended. (Use under these conditions has not been evaluated.) • Wait until the treated area is dry before applying sunscreen, insect repellant, lotion, moisturizer, cosmetics, or other topical medication to the same knee. • Do not use product in combination with an oral

	Patch 1.3%	Gel 1%	Solution 1.5% (Drops)	Solution 2% (Metered Dose Pump)
		• Avoid wearing clothing or gloves for at least 10 minutes after applying gel.		NSAID unless the benefit outweighs the risk, and conduct periodic laboratory evaluations.
Limitations	• Carefully consider the potential benefits and risks of diclofenac patch and other treatment options before deciding to use diclofenac patch. • Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.	—	—	

Sources: Product Information for FLECTOR Patch,[117] VOLTAREN Gel,[118] generic diclofenac 1.5% solution by Apotex,[61] and PENNSAID 2% Solution[62]

Special Populations (Adults)

	Patch	Gel	Solution 1.5%	Solution 2%
Elderly	• Insufficient data in clinical trials • No differences in responses vs. younger pts in clinical experience • May be useful to monitor renal function	• No overall differences in responses vs. younger pts in clinical trials • May be useful to monitor renal function	• No age-related difference in incidence of adverse events • No difference in incidence of adverse events with long-term exposure to solution • May be useful to monitor renal function	• Same as for solution 1.5%
Pregnancy	• Category C prior to 30 wks gestation; category D starting at 30 wks gestations • Effects on labor and delivery are unknown	• Category C • Avoid in late pregnancy • Effects on labor and delivery are unknown	• Same as for patch	• Same as for patch
Lactation	• Whether drug is excreted into human milk is unknown • Discontinue nursing or the drug; weigh risks/benefits of drug to mother	• Same as for patch	• Same as for patch	• Same as for patch
Renal Impairment	• Not recommended in advanced renal disease (not studied)	• Not recommended in advanced renal disease (not studied) • If gel tx is initiated, close monitoring of renal function is advisable.	• Same as for gel	• Same as for gel
Hepatic Impairment	• Discontinue therapy if pt develops persistent or worsening abnormal liver tests or clinical signs/symptoms of liver disease • No recommendations for use of patch in pts w/ hepatic impairment at baseline	• Same as for patch	• Same as for patch	• Same as for patch
Pharmacogenetics/genomics	• No information	• No information	• No information	• No information

Projected Place in Therapy

OA is a heterogeneous group of conditions characterized by focal and progressive biochemical breakdown of the hyaline cartilage of synovial joints and associated changes in the entire joint, including subchondral bone and synovium.[63] The term degenerative joint disease may now be inappropriate to use when referring to OA, since abnormal mechanics and inflammation also seem to be important contributing pathogenic mechanisms of OA.[63] The Agency for Health care Research and Quality (AHRQ) and the Centers for Medicare and Medicaid Services (CMS) consider OA, the most common type of arthritis, to be a priority condition because of its prevalence and high cost in the US.[64] According to CDC data, an estimated 26.9 million adults were affected by OA in 2005 in the US, with a prevalence of 33.6% (12.4 million) of persons 65 years and older and 13.9% of those 25 years and older.[65] The CDC reported that knee OA was estimated to occur in 47.8% of women ≥ 60 years in one study and 37.4% of men and women ≥ 60 years (42.1% female, 31.2% male) in another study.[65] The average direct costs of OA per person has been estimated to be about $2600 per year, and total (direct and indirect) annual costs have been estimated to be about $5700 (FY2000). Job-related OA costs have been estimated to be $3.4 to $13.2 billion per year. In noninstitutionalized adults, OA of the knee is 1 of 5 leading causes of disability,[65] and OA is the leading cause of chronic disability in persons older than 70 years.[63]

Acute minor musculoskeletal injuries such as sprains and strains are common conditions. They can occur in both the upper and lower extremities, although the ankle is the most common site of sprains, and the back and hamstring are common sites of strains.[66] Ankle sprain injuries presenting to emergency departments (2002–2006) occurred at an incidence of 2.15 per 1000 person-years in the US, according to data from the National Electronic Injury Surveillance System (NEISS).[67] Ankle sprain injuries are more common in females, younger age groups and indoor or court types of athletic activity.[67,68] In US Armed Forces, almost 20,000 new incident cases of acute arm and shoulder injuries occurred each year from 2003 to 2012.[69] Acute sprains accounted for the highest number of such injuries, with incidence rates (per 1000 person-years) increasing from 3.9 in 2003 to 8.7 in 2010, then decreasing to 7.7 from 2010 to 2012.

The U.S. has lagged behind Europe and other countries in the use of topical NSAIDs for rheumatic diseases and acute musculoskeletal pain, mainly because none had been marketed in the U.S. until the approval of the diclofenac epolamine patch in 2007. Topical rubifacients (salicylates), topical capsaicin, and other topical balms (e.g., menthol) remain popular choices because of their low cost and wide availability without prescription in pharmacies. However, several international guidelines on the treatment of osteoarthritis,[70] including ones specifically for the hand,[71] hip[72] and knee,[72,73] note that there is a lack of evidence to support the use of topical rubifacients, whereas topical NSAIDs are one of only six evidence-based therapies.

Clinical practice guidelines recommend topical NSAIDs for OA of the hand or knee as a first-line therapy either before oral agents (2 guidelines[70,96]) or as an alternative to acetaminophen (3 guidelines[97,102,104]); as an alternative or adjunct to oral NSAIDs (3 guidelines[97,102,104]); or as a treatment alternative for certain subgroups according to risk factors for NSAID-related harm (2 guidelines[98,102]) or a combination of disease extent and co-morbidities (1 guideline[104]). The VA/DoD clinical practice guideline recommends topical NSAIDs as a treatment alternative to oral NSAIDs for knee OA.[105] (See Table 14, page 30.) Two guidelines on pain pharmacotherapy in geriatric populations suggested topical NSAIDs as alternatives to oral NSAIDs for localized pain. (See Table 15, page 33.) The most recent guideline (published in 2011) pertaining to musculoskeletal injuries recommended topical NSAIDs for Achilles tendinosis, plantar heel or ankle sprain (Table 16, page 33).[74] In several cardiology guidelines, the supporting data on the cardiovascular risks of NSAIDs came from oral NSAID trials.[75,76,77] The cardiology guidelines did not indicate whether topical NSAIDs have a safety advantage over oral NSAIDs (Table 17, page 33). Guidelines on management of acute upper GI bleeding also do not differentiate between topical and oral NSAIDs (Table 18, page 34).[78,79,80] Although the prescribing information does not contraindicate topical NSAIDs in patients with kidney disease, guidelines on management of chronic kidney disease advise avoiding NSAIDs in patients with a GFR less than 60 ml/min/1.73 m^2 who have a serious intercurrent illness (Table 19, page 34).[81,82]

An important caveat to practice guideline recommendations that place topical diclofenac as an alternative first-line therapy in OA is that the currently available evidence applies mainly to short-term (≤ 12 weeks) therapy in patients who are not at high risk for NSAID-related gastrointestinal or cardiovascular harms, for whom less costly orally administered NSAIDs (with antiulcer drugs if indicated) may be carefully considered if NSAID therapy is deemed necessary. For patients who are at high risk for NSAID-related gastrointestinal or cardiovascular harms and require NSAID therapy following trials of alternative therapies for chronic pain due to localized osteoarthritis in a few joints, topical diclofenac gel or solution could be considered preferable to oral NSAIDs, based on their safety profile in patients with risk factors and on lower systemic exposure. However, providers should take into consideration that there have been no safety studies longer than 12 weeks in at-risk patients and no trials comparing topical diclofenac with oral NSAIDs in patients at high risk. Topical diclofenac may be preferred over the formulary topical rubefacients because of their greater evidence of safety and efficacy.

The quality of evidence is high for the efficacy of topical diclofenac in OA and acute musculoskeletal pain. Indirect evidence suggests that diclofenac solution may be associated with a higher risk for application site reactions than the other topical formulations. The quality of evidence is low to moderate for the safety of topical diclofenac. The relative safety of topical diclofenac in patients with pre-existing significant risk factors for serious adverse events (e.g., history of gastrointestinal bleeding or perforation) has not been established. Further studies are needed to assess the cardiovascular and renal risks of topical diclofenac relative to oral NSAIDs and to assess the long-term safety of topical diclofenac relative to oral NSAIDs. None of the studies involved US Veteran populations, so the applicability of the study results to VHA patients carries some uncertainty; however, there is no compelling reason to avoid trying topical diclofenac products in Veterans.

Based on the evidence from trials involving patients with localized OA, topical diclofenac may provide similar efficacy to oral NSAIDs with moderate improvement in safety, mainly reduction in the risk of nonserious GI adverse events. One tradeoff with topical diclofenac is an increased risk of application site reactions, which may be intolerable for some patients and more likely with the DMSO-based solution products than the patch or gel. Another important consideration is the relatively high acquisition cost of topical diclofenac, particularly given the similar efficacy to oral NSAIDs and only moderate improvement in safety.

VA Pharmacy Benefits Management prescription claims data suggest that the gel is the most commonly used topical diclofenac product and that it is used on an as-needed (p.r.n.) basis. The quantity supplied on the initial prescription of topical diclofenac may be limited to one unit (e.g., one 100-gram tube of the gel) to determine whether the product is effective and tolerated. Quantities can be adjusted to reflect patient requirements, which is most commonly one or two tubes per month. Nonpharmacologic therapies, including psychosocial therapies and cognitive behavioral therapy, are safe and effective modalities and should be used concomitantly with pharmacologic therapies for treatment of osteoarthritis.

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Appendices

Abbreviations Used in Appendix Tables

AE	Adverse events
AMSP	Acute musculoskeletal pain
APAP	Acetaminophen
AS	Application site
ASA	Aspirin
ASTEAE	Application site treatment-emergent adverse event
C/CVD	Cerebrovascular or cardiovascular disease
CM	Comorbidity
CMBN	Combination
CSA	Clinically significant abnormal
CTRL	Control
CV	Cardiovascular
DB	Double-blind
DD	Double-dummy
DIC	Diclofenac (oral)
DMSO	Dimethylsulfoxide
DSG	Diclofenac sodium gel
DTS	Diclofenac topical solution
GI	Gastrointestinal
HTN	Hypertension
ITT	Intent-to-Treat
LET	Liver enzyme test
MC	Multicenter
mITT	Modified intent-to-treat
ND	Not done
NL	Normal
NOS	Not otherwise specified
NR	Not reported
NSD	No statistically significant difference
OA	Osteoarthritis
OAHa	Osteoarthritis of the hand
OAK	Osteoarthritis of the knee
OLE	Open-label extension
OS	Observational study
PBO	Placebo
PGA	Patient Global Assessment
PP	Per-Protocol
R_B_W_A_	Randomization, blinding, withdrawals, allocation
RCT	Randomized clinical trial
SAE	Serious adverse event
SRMA	Systematic review / meta-analysis
oNSAID	Oral nonsteroidal anti-inflammatory drug
TEAE	Treatment-emergent adverse event
tNSAID	Topical nonsteroidal anti-inflammatory drug
TRAE	Treatment-related adverse event
UGIB	Upper gastrointestinal bleeding
UHD	Ulcer healing drug
ULN	Upper limit of normal
VEH	Vehicle
WDAE	Withdrawal due to adverse event
WOMAC	Western Ontario and McMaster Universities Index

Appendix 1: Efficacy–Safety Trials: Osteoarthritis (OA)

Head-to-Head Trials in OA

No head-to-head trials that compared topical diclofenac formulations for OA were found.

Active Comparator Trials in OA

Topical Diclofenac Gel vs. Oral Ibuprofen in OA

Diclofenac 1% Emulgel (10 cm applied 4 times daily) was shown to be no worse than, and at least equivalent to, **oral ibuprofen** (400 mg 3 times daily) administered for 21 days in a 34-center, double-blind, double-dummy, randomized trial which was published in German in 2001 and abstracted in an English-language paper in 2008 by the same author.[83]

Table 3 Diclofenac Gel Versus Oral NSAID in Osteoarthritis

Study	Design	Interventions (N)	Efficacy Outcomes†	Incidence of Local Skin Reactions	Incidence of GI Adverse Events	Other Adverse Events	Comments
Zacher (2001) *German paper abstracted in Zacher (2008)*[83] ***Error! Bookmark not defined.*** R2 B? W? A0	34-center DB DD RCT, noninferiority, mITT, PP, Germany N = 321 Mean age 60.7 y Males 12% Active OA of finger joints ("Heberden's" or "Bouchard's" OA)	Diclofenac 1% Topical Emulgel (DTG) 10 cm 4x/d (165) Ibuprofen (IBU) 400 mg p.o. 3x/d (156) 3 wk	1 – Responder rate for 40% pain reduction 44% vs. 34% (p = 0.007)	Not reported	Lower with DTG 9% vs. 14%	Any AEs 22% vs. 27% WDAEs related to drug 1.2% vs. 8.3% 1 SAE (ileus) in IBU gp	88% postmeno-pausal women; external validity and generaliz-ability to veterans are uncertain

† Key to Efficacy Outcomes: 1-Pain; 2-Physical Function; 3-Patient Overall Health Assessment (POHA); 4-Patient Global Assessment (PGA). DTG, Diclofenac topical gel.

Diclofenac Topical Solution Versus Oral NSAIDs in OA

Three studies that compared diclofenac topical solution with an oral NSAID showed no significant differences between the two treatments in analgesic efficacy (Table 4).

Table 4 Diclofenac Sodium Topical Solution 1.5% Versus Oral NSAID in Osteoarthritis

Study	Design	Interventions (N), Duration	Efficacy Outcomes†	Incidence of Local Skin Reactions	Incidence of GI Adverse Events	Other Adverse Events	Comments
Simon (2009)[22] Fair quality for DTS vs. PBO Low quality for DTS vs. DMSO, DIC and CMBN	61-center DB DD PC RCT mITT, Canada, US Primary Efficacy Measure was DTS vs. PBO for outcomes 1–3; other	DTS (PENNSAID) 40 drops 4x/d (154) PBO (157) DMSO Vehicle (161) DIC SR 100 mg p.o. 1x/d (151)	DTS vs. DIC: NSD for outcomes 1–4 DTS vs. PBO and DTS vs. DMSO: DTS superior for outcomes 1–4 CMBN vs.	Highest with CMBN followed by DTS (27%, 8%, 17%, 7%, 31%) Mainly dry skin	GI AEs lowest with DTS (6%, 10%, 11%, 24%, 26%)	CV events <2% per tx group HTN – similar (1.2%–1.3% for DTS, DMSO, DIC, CMBN; 0.6% PBO)	No additional analgesic or systemic AEs were seen with CMBN vs. oral DIC Dry skin is attributable to DMSO, which can dissolve

Study	Design	Interventions (N), Duration	Efficacy Outcomes†	Incidence of Local Skin Reactions	Incidence of GI Adverse Events	Other Adverse Events	Comments
R2 B2 W1 A1	comparisons were post hoc analyses N = 775 Mean age ~62 y Males 38% Knee OA	Combined PENNSAID + DIC SR (CMBN; 152) 12 wk	DIC: NSD			Change to above normal (% of pts): ALT 4, 3, 1, 19, 17; AST 7, 4, 5, 20, 14 LETs, increase to ≥ 3x ULN (% of pts) – 0, 0.7, 0.7, 1.4, 2.1 Hg, change to below normal (% of pts): 2, 5, 3, 6, 12 CrCL, change to below normal (% of pts) – 8, 6, 6, 7, 11	lipids on the skin surface
Tugwell (2004)[23] FAIR quality; R2 B2 W1 A1 Mfr sponsored	MC DB DD Equivalence RCT, PP and ITT, Canada N = 622 (311 per tx group) Mean Age 64 y ≥ 75 y: 16% Male 43% Knee OA	PENNSAID 50 drops (1.55 ml) to knee 3x/d (total 4.6 ml or ~75 mg drug) DIC 50 mg p.o. 3x/d (total 150 mg) 12 wk	1 - NSD 2 - Improvement 39% vs. 46% (p = 0.06) 4 - NSD Txs met equivalence criteria	Skin-related WDAEs – Higher with DTS, 10% vs. 0.3% (p < 0.0001)	GI-related WDAEs – Lower with DTS, 6% vs. 16% (p < 0.0001) GI AEs – Lower with DTS, 35% vs. 48% (p < 0.0006) Tx-related severe GI AEs – Lower with DTS, 7.4% vs. 21% (p = 0.002)	Change to abnormal (% of pts): ALT 4% vs. 19%; AST 7% vs. 20%	Numerically LESS (NSD) functional improvement with DTS than DIC p.o.
Di Rienzo Businco (2004)[49] LOW quality; R1 B0 W0 A0	RCT, Italy N = 36 (18 per tx group) Median Age 43 y Male 47% TMJ dysfunction	DTS 16 mg/ml 10 drops 4x/d DIC 50 mg p.o. 2x/d 2 wk	1-NSD 2-NSD	Modest irritation and heat sensation with DTS (n = 3)	GI AEs - Lower with DTS: Epigastralgia 6% vs. 89% Epigastric burning 0% vs. 67% Retrosternal burning 28% vs. 39%		

DIC, Diclofenac (oral); DTS, Diclofenac sodium topical solution; LET, Liver enzyme test; PEV, Primary Efficacy Variable; TMJ, Temporo-mandibular joint. † Key to Efficacy Outcomes: 1-Pain; 2-Physical Function; 3-Patient Overall Health Assessment (POHA); 4-Patient Global Assessment (PGA) of knee OA

Two large studies showed that, in patients with symptomatic knee osteoarthritis, diclofenac topical solution and oral NSAIDs were comparable in efficacy outcomes including pain and physical function.[22,23] A third, small study involving patients with temporomandibular joint dysfunction also showed similar efficacy between topical and oral diclofenac.[49] In all three studies,

local skin reactions (mainly dry skin) were more common with the topical therapy, whereas gastrointestinal and systemic adverse events were less common with the topical therapy. Two of the studies showed durability of analgesic effects with topical diclofenac over a 12-week period.[22,23]

Topical Diclofenac Versus Topical Non-NSAID in OA

No RCTs were found.

Systematic Reviews / Meta-analyses of Topical Diclofenac Trials in OA

Topical Diclofenac Versus Placebo / Vehicle and Durability of Efficacy for ≥ 4 Weeks in OA

Table 5 Reviews of Topical NSAID Therapy ≥ 4 Weeks in Duration in Osteoarthritis

Study	Design	Interventions (N)	Efficacy Outcomes†	Incidence of Local Skin Reactions	Incidence of GI Adverse Events	Other Adverse Events	Comments
Biswal (2006; NICE)[21] Study quality and statistical methods were unclear.	SRMA of RCTs ≥ 4 wks in duration comparing any tNSAID with PBO/VEH K = 4 N = 709 Knee OA	Diclofenac Solution (K = 2; N = 247) Eltenac Gel (K = 2; N =183) PBO (K = 3; N = 222) DMSO VEH (K = 1; N = 159) 4–12 wks	1–Mean ES -0.28 (95% CI -0.42 to -0.14) [small] No correlation between ES and duration of tx	—	—	—	**CONCLUSION:** Topical NSAIDS are effective for pain relief in knee OA for a longer duration; however, this may not hold true for all NSAID preparations.

† Key to Efficacy Outcomes: 1-Pain; 2-Physical Function; 3-Patient Overall Health Assessment (POHA); 4-Patient Global Assessment (PGA). DTG, Diclofenac topical gel.

Topical Diclofenac Versus Oral NSAIDs in OA

A 2010 systematic review of short-term studies (< 6 months) showed no significant analgesic differences between oral and topical NSAIDs in adults with chronic pain related to osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain or ankylosing spondylitis.[51] The review also showed that topical diclofenac was "gastroprotective" (pooled RR from 2 RCTs: 0.47; 95% CI 0.18–1.23) but there was statistically significant heterogeneity between the trials. Topical diclofenac therapy had a greater risk of application site dryness relative to oral NSAIDs (24% vs. 2%; pooled RR 12.02; 95% CI 3.96–36.54). Withdrawals due to adverse events were similar between topical and oral diclofenac groups (17% vs. 21%).

A 2012 Cochrane systematic review / meta-analysis found good-quality evidence supporting the efficacy and safety of topical diclofenac in the treatment of moderate to severe chronic pain due to osteoarthritis of the hands or knees.[52] The proportion of participants experiencing clinical success was 55% for topical NSAIDs and 54% for oral NSAIDs (relative benefit, 1.02; 95% CI 0.94 to 1.1). The findings from 5 RCTs also showed that topical NSAIDs (N = 846) were more likely than oral NSAIDs (N = 805) to be associated with local adverse events (NNH 6.4; 95% CI 5.3 to 8.0). Oral NSAIDs were more likely than topical NSAIDs to be associated with GI adverse events (NNH 10; 7.6 to 17; 6 RCTs; N = 1011 for topical, 950 for oral). There was no significant difference between topical NSAIDs and oral NSAIDs in rates of withdrawals due to adverse events in indirect comparisons (6 RCTs; N = 1011 for topical NSAID, 950 for oral NSAID). Withdrawals due to lack of efficacy were 7% (range, 1% to 10%) with topical NSAIDs (N = 603) and 3% (range, 2% to 3%) with oral NSAIDs (N = 594) among 3 RCTs (NNT 23; 14 to 52). The authors concluded that topical diclofenac is about as effective as oral diclofenac, and probably as effective as other oral NSAIDs, for hand or knee OA and, based on good evidence, has a lower incidence of GI and other systemic adverse events. The authors suggested that topical diclofenac would make a useful first-line therapy, particularly in older patients who may be more susceptible to GI harm from oral NSAIDs. Although the authors believe their data is complete for PENNSAID solution, the limitations of the evidence include potential incompleteness of data (unpublished studies) and publication bias. More data comparing topical and oral NSAIDs are needed on the risks of rare

but serious harms such as GI bleeding, cardiovascular events or renal failure. The 2012 Cochrane review showed similar findings to those of a 2011 systematic review by Chou, et al.[84].

Comparison of Different Topical Diclofenac Formulations in OA

The 2010 systematic review mentioned above showed that, compared with placebo, the 1.5% topical solution of diclofenac (1 RCT) but not the gel (2 RCTs), had an increased incidence of withdrawals due to adverse events (6% vs. 0%; RR 11; 1.34 to infinity; NNH 17).[51] Relative to placebo, the solution had an increased risk of dry skin (36% vs. 1%; relative risk (RR) 30; 95% CI 5.44 to 172.22; NNH 3), whereas there was no significant difference between the 1% topical gel formulation and placebo in the rates of application site reactions. Neither the solution nor the gel increased GI adverse events compared with placebo. Indirect comparison of efficacy between diclofenac solution 1.5% (3 RCTs) and gel 1% (2 RCTs) could not be done because of heterogeneity in the reporting of results.

The 2012 Cochrane systematic review / meta-analysis also suggested that one cannot conclude that there are differences in the analgesic efficacy of different topical diclofenac formulations.[52] NNTs for clinical success (defined as a 50% reduction in pain, or an equivalent measure such as a "very good" or "excellent" global assessment of treatment, or "none" or "slight" pain on rest or movement) were 5.0 relative to placebo (95% CI 3.6 to 7.8) with diclofenac patch or gel (pooled data) at 2 to 3 weeks; 5.2 (3.5 to 11) with diclofenac solution at 4 to 6 weeks; and 10 (7.3 to 17) with diclofenac solution or gel (pooled data) at 8 to 12 weeks. Part of the variation in NNTs that was seen according to duration of studies may have reflected differences in study quality (the shorter term studies were smaller and of poorer quality than those of the longer-term trials). In indirect comparisons of formulations, the NNT for clinical success was 6.4 (4.6 to 10) with solution and 11 (7.7 to 17) with gel over 8 to 12 weeks (no statistically significant difference.

A 2015 network meta-analysis that compared the efficacy of pharmacologic treatments for osteoarthritis did not include studies evaluating topical NSAIDs / diclofenac.[85]

Efficacy–Safety Trials: Musculoskeletal Pain (MSP)

Head-to-Head Trials in MSP

No RCTs were found.

Active Comparator Trials in MSP

No RCTs were found.

Systematic Reviews / Meta-analyses of Topical Diclofenac Trials in MSP

Two multicenter, placebo-controlled, randomized trials[86,87] evaluating diclofenac patch 1.3% (one patch daily for 7 days) were included in meta-analyses[88] which showed that topical NSAIDs as a class were efficacious for **acute ankle sprains**. In one study, the difference between diclofenac patch and placebo in the reduction of pain on movement from baseline to Day 3 on a 100-mm Visual Analog Scale (VAS) was -5.06 mm [95% CI -8.57, -1.55; p = 0.005], in favor of diclofenac patch.[86] In the other study, the difference between diclofenac patch and placebo in the reduction in spontaneous pain from baseline to Day 7 was 4.8 mm on a 100-mm VAS.[87] The percentage of patients with at least 30% reduction in pain (VAS-30) became significantly better with diclofenac patch than placebo starting 4 hours after application (NNT 5; p = 0.01) and persisted for 2 days. Neither study showed significant treatment differences in edema measures.

Pooled analyses of two additional studies of similar design (total N = 274) also showed superior efficacy with diclofenac patch (one patch daily for 7 days) over placebo.[89] The difference between treatments in the reduction in pain on movement from baseline to Day 7 was 7 mm on a 100-mm VAS. VAS-30 was achieved by 91% of patients on diclofenac patch and 71% on placebo (NNT = 5; p = 0.0001). Results for reduction in swelling were inconsistent; one trial showed a significant treatment benefit, whereas the other trial showed no significant treatment difference.

Topical Diclofenac Versus Oral NSAIDs in MSP

The authors of a 2013 Cochrane systematic review / meta-analysis of studies evaluating NSAIDs in adults with lateral elbow pain found no studies comparing topical diclofenac with oral NSAIDs.[90] The results showed that topical diclofenac had an analgesic effect (NNT of 7 relative to placebo over a treatment period of 10 days to 4 weeks; 95% CI 3–21). However, these results were not robust when skewed data from 2 of the 3 trials were excluded from the meta-analysis. Although the

remaining trial and 2 other trials that could not be included in the meta-analysis all showed favorable results with topical diclofenac, the authors concluded that the benefits or harms of topical or oral NSAIDs in adults with lateral elbow pain are unclear because of the limited evidence available.

In a 2015 updated Cochrane systematic review / meta-analysis of studies on various topical NSAIDs in adults with acute musculoskeletal pain, none of the included studies compared topical diclofenac with an oral NSAID.[24] The authors concluded that topical NSAIDs can provide good analgesic effects probably similar to those of oral NSAIDs for acute musculoskeletal pain such as sprains, strains and overuse injuries, and topical NSAIDs do not increase the incidence of local adverse reactions or cause systemic or gastrointestinal problems typically seen with oral NSAIDs.

Comparison of Different Topical Diclofenac Formulations in MSP

The 2015 updated Cochrane review also found diclofenac gel to be significantly better than the patch in indirect comparisons for the treatment of acute musculoskeletal pain.[24] Diclofenac gel (VOLTAREN EMULGEL) had an NNT of 1.8 (95% CI 1.5–2.1; 2 RCTs, N = 314) and diclofenac (FLECTOR / DHEP) plasters / TISSUGEL had an NNT of 4.7 (3.7–6.5; 4 RCTs, N = 1030) for at least 50% reduction in pain intensity ($p < 0.00001$).

Systematic Reviews / Meta-analyses of Long-term Effectiveness Studies in MSP

No long-term effectiveness studies were found.

Appendix 2: Selected NSAID-related Adverse Events

Major safety concerns with oral NSAIDs include increased risk of thromboembolic cardiovascular and cerebrovascular events, increase in blood pressure, hepatotoxicity, nephrotoxicity, gastrotoxicity (i.e., irritation, ulceration, bleeding and perforation), fluid retention, peripheral edema, anemia, asthma exacerbation and severe allergic reactions.

Selected Adverse Events in Short-term Trials

Selected safety findings from controlled trials supporting the FDA's marketing approval of the topical diclofenac products are summarized in Table 6.

Table 6 Pooled, Selected Serious and Nonserious Adverse Events Across Phase III RCTs by Diclofenac Product

	Patch 1.3% (N = 572) vs. PBO (N = 564)	Gel 1% (N = 913) vs. VEH (N = 876)	Solution 1.5% (N = 911) vs. 2.3% DMSO PBO (N = 332) vs. DMSO VEH (N = 603) vs. o-Diclofenac (N = 462) vs. CMBN (N = 152),	Solution 2% (N = 131) vs. VEH (N = 129)
	AMSP K = 4, 1–2 wk	OAKHa K = 4, 8–12 wk	OAK K = 7, 6–12 wk	OAK K = 1, 4 wk
Adverse Event Category	**%**	**%**	**%**	**%**
Serious Adverse Events	*0.0 / 0.2*	*1 / 1*	*1 / 1.5 / <1 / 1 / 2*	*0 / 0*
Cerebrovascular Thrombosis SAE	NR	NR	0.2 / 0.3 / 0.0 / 0.0 / 0.6	NR
Coronary Thrombosis SAE	NR	NR	0.2 / 0.0 / 0.0 / 0.2 / 0.6	NR
Gastrointestinal SAE	NR	Total NR	0.0 / 0.0 / 0.2 / 0.4 / 0.0‡	NR
Increased LETs– SAE	NR	NR	0.0 / 0.0 / 0.0 / 0.2 / 0.0	NR
Withdrawals due to AEs	*3 / 3*	*4.9 / 2.7*	*13 / 10 / 6 / 21 / 15*	*3 / 4*
Gastrointestinal WDAE	1.0 / 0.5	NR	3 / 1 / 1 / 13 / 4	NR
AS Reaction WDAE	2.4 / 1.6	NR	6 / <1 / 1 / <1 / 4	1.5 / 6.2
Cardiovascular WDAE	NR	NR	<1 / <1 / <1 / <1 / 1	0.8 / 0.0
Other WDAE	NR	NR	4 / 8 / 3 / 8 / 6	NR
Nonserious AEs	*29 / 30*	*49.8 / 44.2*	*NR*	*40.0 / 45.7*
Dermal: AS AE	11 / 12†	6.8 / 2.1	NR	31.5 / 38.8
AS Dermatitis	1.6 / 0.5	3.5 / 0.7	9 / 2 / 4 / 1 / 8	NR

AS Dry skin	NR	0.4 / 0.3	32 / 5 / 20 / 2 / NR	21.5 / 21.7
AS Dermatitis w/vesicles			2 / 0 / NR / NR / NR	
Gastrointestinal AE	9 / 6	NR	NR	NR
Rectal hemorrhage	NR	NR	0.1 / 0.3 / 0.0 / 0.2 / 3.3	NR
Melena	NR	NR	0.5 / 0.3 / NR / 2 / NR	NR
Cardiovascular AE	NR	~ PBO	Total NR	NR
Renal AE	NR	~ PBO	NR	NR
Hepatic AE	NR	~ PBO	Total NR	NR
Laboratory Abnormalities				
ALT 3 x ULN – AE	Labs ND	0.2% / 0.1%	2 / 0.6 / NR / 8 / 7	NR

Sources: FDA Medical Reviews for each product[1,112,116,92]
† "Application Site Conditions"; ‡ Upper GI bleed (n = 1) and lower GI bleed (n = 1) on o-diclofenac; enteritis (n = 1) on vehicle control.
AE, Adverse event (nonserious); AMSP, Acute musculoskeletal pain; AS, Application site; ND, Not done; NR, Not reported; OAHK, Osteoarthritis of hip/knee; OAKHa, osteoarthritis of knee/hand; SAE, Serious adverse event

A 2011 pooled analysis of 14 short-term (6–14 days) placebo-controlled trials evaluating **diclofenac patch** showed no significant differences between diclofenac patch and placebo in the rates of gastrointestinal events (3.4% vs. 2.9%, respectively; N = 890 and 893, K = 10).[91] Subgroup analyses showed no sex- or age-related treatment differences in gastrointestinal events. There were no cases of gastrointestinal bleeding or perforation.

In the major efficacy trials of **diclofenac gel**, 24 (2.6%) of 912 diclofenac gel patients and 34 (3.9%) of 876 placebo patients used a prohibited oral NSAID.[1] Overall, arthralgia was the only common adverse event (frequency of ≥ 1% in either the knee or hand major trial) that occurred at a higher rate in the **diclofenac gel** group (6/913, 0.7%) than the placebo group (3/876, 0.3%). The adverse event profile did not suggest a synergistic or additive toxicity with concomitant oral NSAID use. Notable was the absence of gastrointestinal and cardiovascular events among the common adverse events.

Additional findings for selected adverse events from the FDA's evaluation[92] that compared topical **diclofenac solution** with oral diclofenac and combination therapy are summarized in Table 7.

Table 7 Selected Adverse Events with Diclofenac Solution 1.5%, Pooled Data from Controlled Phase III Trials

Adverse Event	Findings
Cardiovascular / Cerebrovascular Thrombotic Events	Diclofenac solution and oral diclofenac were similar in incidence of cardiovascular events. The numbers of cases were too small to assess the risk of these adverse events during treatment and to evaluate whether there was a difference in risk among the 1.5% solution, placebo, oral diclofenac and combination treatment with solution plus oral diclofenac.
Gastrointestinal / Gastrointestinal Bleeding	Gastrointestinal adverse events for the 1.5% solution, oral diclofenac, and the combination of solution with oral diclofenac, respectively, included dyspepsia (8%, 19% and 3%), abdominal pain (6%, 17% and 2%), flatulence (4%, 11% and 0%), diarrhea (4%, 13% and 8%), nausea (4%, 10% and 3%), and constipation (3%, 7% and 1%). According to the FDA medical review, gastrointestinal adverse events occurred less frequently in the diclofenac solution 1.5% group than in the oral diclofenac group.[92]
Renal Impairment	No renal adverse events were reported. Smaller numerical increases from baseline to 12 weeks in mean serum creatinine were seen with the topical diclofenac solution than oral diclofenac and the combination treatment (0.06, 3.2 and 4.4 micromol/L, respectively); however, changes from normal to clinically significantly abnormal values were uncommon and incidences of these changes were similar among the treatments (0 to <1%). Urinalysis results showed an increased number of patients with hematuria in the diclofenac solution group; this was considered to be a **safety signal** that required further studies of longer duration.
Hepatotoxicity	The incidences of changes in ALT from normal to clinically significant abnormal values favored topical diclofenac over oral diclofenac and the combination treatment (<1%, 3% and 5%, respectively).
Decreased Hemoglobin	Mean decreases in hemoglobin from baseline to 12 weeks also favored diclofenac solution 1.5% over oral diclofenac and the combination (–0.01, –2.7 and –4.8 g/L); however, the incidences of changes in hemoglobin from normal to clinically significantly abnormal were similar among the treatment groups (<1 % each).

In the pooled results, rectal hemorrhages including bleeding hemorrhoids were observed in 3.3% of 152 patients in the combination therapy group, and 0.1% of 911 patients in the diclofenac solution group, 0.2% of 462 patients in the oral diclofenac group, 0.3% of 332 patients in the placebo group, and 0.0% of 603 patients in the vehicle control group.[92] The risk of these adverse events may be increased by concomitant use of topical and oral diclofenac, particularly in patients with

predisposing factors (e.g., hemorrhoids, diverticulosis). Topical diclofenac solution alone may be associated with a risk of rectal hemorrhage similar to that seen with oral diclofenac.

The FDA medical review noted that, relative to oral diclofenac, the combination of diclofenac solution 1.5% and oral diclofenac had higher rates of gastrointestinal symptoms (including rectal bleeding), edema, severe skin reactions, increases in creatinine, urea, liver enzymes and decreased hemoglobin and hematocrit.[92] These findings suggested that topical diclofenac solution 1.5% added to the adverse events of oral diclofenac.

Selected Adverse Events in Long-term Safety Studies

Two published, observational extension studies evaluated the safety and tolerability of diclofenac solution 1.5%.[93,94] There were no deaths or serious adverse events. One of the studies reported that cardiovascular events occurred in 9.1% of patients, including hypertension in 3.5%, but did not report any thromboembolic cardiovascular or cerebrovascular events.[94]

Table 8 Selected Adverse Events with Diclofenac Solution 1.5%, Extension Studies

	Findings, Treatment Duration	
Adverse Events	**9 to 12 Months (N = 578)**	**2 Days To 16 Months (N = 793)**
Cardiovascular / Cerebrovascular Thrombotic Events	0%	NR
Gastrointestinal / Gastrointestinal Bleeding	Nausea, gastroenteritis, or hiatal hernia 0.5%	Any GI event 12.0% Abdominal pain 2.3%
Renal Impairment	SCr Increased 0.2%	SCr Increased 2.4% NL to CSA SCr 0.1%
Hepatotoxicity	Abnormal LFT or ALT Increased 0.3%	NL to CSA ALT 0.3%
Decreased Hemoglobin	—	NL to CSA 0.3%

Sources: [93,94]

CSA, Clinically significant abnormal; NL, Normal; TRAE, Treatment-related adverse event

Selected Adverse Events in Older Patients and Other Patients with Risk Factors

Short-term Safety Studies

Five short-term studies evaluated the safety of topical diclofenac products according to patient risk factors for adverse events (Table 9).

Table 9 Short-term Safety Studies of Topical Diclofenac Products in Patients with Risk Factors

<table>
<tr><th>Reference,
Design, Methods, Population</th><th>Results</th><th>Authors' Conclusions
Study Limitations</th></tr>
<tr>
<td>Makris, et al. (2010)[53]

Systematic review of English-language RCTs 2–12 wks in duration, case reports, OSs, letters, editorials or dissertations reporting AEs from tNSAIDs in older adults (≥60 yo) with OA (mainly of the knee)

K = 19 (inc 16 RCTs, N = 4428 randomized, 2043 to tNSAID; 10 of 16 RCTs scored 5/5 on Jadad scale)

9% to 48% men; mean age range 60–67 y

8 RCTs excluded risk factors for oNSAID toxicity (e.g., corticosteroid use, renal, hepatic and/or peptic ulcer disease, GIB within 3 y of study)
11 RCTs involved topical diclofenac (1 each for 1%, 1.16% and 2% gel, 2 for patch, and 6 for 1.5% solution)
14 RCTs allowed APAP
6 RCTs allowed ASA ≤325 mg/d for CV prophylaxis

Case reports/series: 5 subjects were anticoagulated for cardiac valve replacements and 1 had chronic venous leg ulcers</td>
<td>Most frequently reported application site adverse events (AEs): dry skin, erythema, irritation, paresthesias and pruritus, particularly among the tNSAID, VEH and PBO groups.
Selected Application Site AEs among RCTs, % Range
<table>
<tr><th>AE</th><th>TOP</th><th>PO</th><th>VEH</th><th>PBO</th></tr>
<tr><td>Dry skin</td><td>0.79–39.3</td><td>1–2.6</td><td>11.2–25.3</td><td>1–3.2</td></tr>
<tr><td>Rash NOS</td><td>0.8–13</td><td>0–2</td><td>1.2–13.9</td><td>0</td></tr>
<tr><td>Rash*</td><td>1.4–21</td><td>0–13.6</td><td>—</td><td>0–16.5</td></tr>
<tr><td>Dermatitis</td><td>0–4.8</td><td>0.7–1</td><td>3.1</td><td>0–0.6</td></tr>
</table>
*Rash grouped as erythema, irritation, "local effects," exanthema

Most frequently reported systemic AEs: GI and headache (topical and oral NSAID groups).
Anemia, LFT and renal abnormalities, and "severe" GI AEs (defined as events that produced significant impairment of functioning or incapacitation and were a definite hazard to patient's health) were higher in the oral NSAID group.
Selected Systemic AEs among RCTs, % Range
<table>
<tr><th>AE</th><th>TOP</th><th>PO</th><th>VEH</th><th>PBO</th></tr>
<tr><td>UGI NOS</td><td>10.3</td><td>8.5</td><td>—</td><td>—</td></tr>
<tr><td>GI NOS</td><td>2.6–4.8</td><td>0.8–13.4</td><td>—</td><td>7.3</td></tr>
<tr><td>Abd pain</td><td>1.4–12</td><td>3–22</td><td>0.9–3.1</td><td>0.6–2.4</td></tr>
<tr><td>Dyspepsia</td><td>0.7–15</td><td>3–26</td><td>0.9–5</td><td>0.8–6</td></tr>
<tr><td>GI Bleed*</td><td>0–1</td><td>0–2</td><td>0–1.2</td><td>0</td></tr>
<tr><td>LFT abnl</td><td>0–6.9</td><td>7.9–19.6</td><td>1.3–5.3</td><td>0.6–4.2</td></tr>
<tr><td>CrCl abnl**</td><td>0–7.6</td><td>7.2–10</td><td>6</td><td>0–5.7</td></tr>
<tr><td>∆ in Hg</td><td>0–2.1</td><td>5.8–10</td><td>3.3</td><td>4.9</td></tr>
<tr><td>Headache</td><td>5–17.5</td><td>6–17.2</td><td>4.3–13</td><td>11.5</td></tr>
</table>
*GI bleed includes melena and rectal hemorrhage. **% of pts changing from normal to abnormal CrCl (ml/min). Bolded rows indicate that topical and oral NSAID % ranges do not overlap.

Withdrawals due to AEs were similar between topical and oral NSAIDs.

Withdrawals from RCTs, % Range
<table>
<tr><th>Reason</th><th>TOP</th><th>PO</th><th>PBO</th></tr>
<tr><td>AE</td><td>0–21</td><td>0–25</td><td>0–16</td></tr>
<tr><td>Inefficacy</td><td>0–17</td><td>2–3</td><td>0–12</td></tr>
</table>
</td>
<td>AEs may have been related to the vehicle or carrier (e.g., DMSO and its metabolite, dimethyl sulfide) or the buffering agent (isopropanolamine causing contact dermatitis).

"While topical NSAIDs are safer than oral NSAIDs, given the AE profile and withdrawal rates described in this study, further data are needed to quantify the incremental benefits of these agents compared to other treatment modalities for older adults with OA."

Limitations:
• No quantitative analysis
• No subgroup analyses
• RCTs excluded risk groups
• Variable reporting of AEs
• Dose effect not analyzable</td>
</tr>
</table>

Reference, **Design, Methods, Population**	**Results**	**Authors' Conclusions** **Study Limitations**
Roth and Fuller (2012)[54] Pooled safety analysis of 7 US and Canadian MC, blinded, Phase III RCTs (4–12 wks' duration) of diclofenac sodium topical solution (DTS) 1.5% (w/w) in 45.5% DMSO (PENNSAID) in the treatment of OAKHa in a subset of patients **aged 75 years or older.** Excluded corticosteroid use, oral analgesics, and clinically significant renal, hepatic or peptic ulcer disease. Allowed ASA for CV prophylaxis and APAP. K = 7, N = 280 (138 DTS, 39 PBO DMSO 2.33% or 4.55%, 103 Control (CTRL) DMSO 45.5%) Mean age range 77.9–78.4 y % Male range 33.0%–48.7% % HTN at baseline was lowest in PBO group (38.5%) vs. DTS (60.9%, p = 0.013) and CTRL (61.2%, p = 0.015)	Most common TEAEs involved the **skin or subcutaneous tissue**, primarily at the application site, and occurred more commonly on DTS (44.2%, p < 0.0001) and CTRL (30.1%, p < 0.0042) than PBO (7.7%). DTS (36.2%, p <0.0001) and DMSO (18.4%; p = 0.0142) had higher incidences of **dry skin** than PBO (2.6%). **GI AEs** occurred in <18% of pts; no group differences. **CV AEs** were rare (2.2% DTS, 2.6% PBO, 0.0% CTRL); no group differences. **Renal/urinary AEs** were also rare (0.0%, 0.0%, 1.9%) Changes from baseline in **BP, hepatic and renal** "enzyme levels" also showed no group differences. **Serious AEs**: 0.7% DTS, 7.7% PBO and 0.0% CTRL; significantly lower incidence in DTS and CTRL groups than PBO group ($p \leq 0.034$). **WDAEs**: no significant group differences. **Application Site TEAEs**: higher incidence on DTS (39.1%, p < 0.0001) and CTRL (23.3%, p = 0.014) than PBO (5.1%). Specifically, groups differed significantly in the incidence of dry skin. Other ASTEAEs on DTS: Erythema (5.8%) and contact dermatitis (5.1%). Two DTS patients (1.4%) had 3 severe ASTEAEs. No significant group differences in withdrawals due to ASTEAEs (5.1%, 0.0%, 1.9%).	DMSO contributes to some of the skin and subcutaneous tissue AEs. "[DTS] appears to be well tolerated in persons aged 75 years or older.... These findings support the new recommendation by the ACR that topical NSAIDs be used for the treatment of hand or knee osteoarthritis in the elderly." Limitations: • Retrospective pooled analysis • Short-term trials (4–12 wk) • Mainly knee OA • Small sample sizes • Limited lab testing • Indirect measures of hepatic and renal toxicity

Reference, Design, Methods, Population	**Results**	**Authors' Conclusions Study Limitations**
Baraf, et al. (2012)[55] Post hoc pooled analysis of data from 8- or 12-wk DB PC RCTs involving patients aged ≥35 years with mild to moderate OAK (K = 3) and patients aged ≥40 years with mild to moderate OAHa (K = 2). Analyzed data by **age and co-morbidities** (HTN, T2DM, and cerebrovascular or cardiovascular disease [C/CVD]). Descriptive statistics. K = 5, N = 1426 (inc. 721 DSG) 35% Male 888 (62.3%) aged <65 y; 538 (37.7%) aged ≥65 y. US, France and Germany For OAK: Diclofenac sodium 1% gel (DSG) 4 g vs. VEH q.i.d. for 12 wks For OAHa: DSG 2 g vs. VEH q.i.d. for 8 wks Allowed APAP for non-OA pain except 24–36 h before assessments.	**Effects of Age**: • Incidence of **≥1 AE** was similar in pts aged <65 y vs. ≥65 y (56.6% vs. 55.8% for OAK and 39.1% vs. 42.7% for OAHa). • **GI, CV, and renal AEs (including hematuria)** were rare and incidences were similar between DSG and VEH in comparisons made by age or co-morbidities. There were no reports of heart failure (HF). • **Hepatic AEs** had similar incidences in DSG and VEH groups in younger and older pts (no data given for effects of co-morbidities). • **Application site reactions** were the main reason for the higher frequency of AEs with DSG than VEH. • **WDAEs** were more frequent with DSG than VEH… – In older patients (3.6% vs. 0.4%) and younger patients (2.9% vs. 0.9%) with OAK, mainly because of different rates of withdrawals due to application site dermatitis. – In older patients (4.3% vs. 1.2%), but not in younger patients (0.9% vs. 0.9%) with OAHa. The difference in older patients was mainly due to a higher rate of withdrawals due to application site reactions or allergic dermatitis on DSG than VEH (3.2% vs. 1.2%). **Effects of Co-morbidities:** • Among DSG-treated patients, the incidence of ≥1 AE was similar in younger and older pts and in pts with and without each co-morbidity or two co-morbidities in all comparisons, except the incidence of ≥1 AE was – Lower in pts with vs. without T2DM in OAHa (28.0% vs. 41.6%) – Higher in pts with vs. without C/CVD in OAHa (48.5% vs. 39.2%) • Among patients who received DSG, none with C/CVD had a CV or renal AE. There were no reports of HF. • No DSG treated diabetic patient had a renal AE. • The only CV AE considered potentially treatment related was a DVT, which occurred in an 80-year-old woman with HTN and T2DM. • No other patient with multiple comorbidities experienced a CV or renal AE.	DSG seemed to be generally well tolerated by patients aged <65 years and patients aged ≥65 years as well as patients with HTN, T2DM, and/or C/CVD. Topical NSAID therapy maybe an appropriate option in patients with localized pain in a few joints for whom oral NSAIDs may present an unacceptable risk of AEs. Limitations: • Short trial durations (8 or 12 wk) • Excluded pts w/ severe co-morbidities • No statistical analyses (study not designed to provide sufficient power to compare subpopulations).
Peniston, et al. (2013)[56] Post hoc analysis of a 12-wk DB VC RCT in pts with mild to moderate OAK pain, comparing AEs in pts who did or did not receive concurrent meds known to have a drug-drug interaction (DDI) with diclofenac. Excluded pts with active PUD, h/o GIB or other clinically significant medical disease. DSG 4 g 4x/d x 12 wk vs. PBO N = 254 DSG; 171 received drug w/potential DDI w/diclofenac, mostly antihypertensives, antidepressants and anti-inflammatories, and 83 did not receive an interacting co-medication. DSG group: 32.7% males, 75.2% white; mean age 59.7 y (36–90).	**TEAEs** in ≥10% of either DDI group or non-DDI group: Any AE 62.6% vs. 55.4% Headache 16.4% vs. 8.4% Arthralgia 15.8% vs. 8.4% Back pain 8.2% vs. 10.8% **GI AE**: 5.3% vs. 7.2% **CV AE***: 4.7% vs. 1.2% HTN 2.3% vs. 0.0% **Renal AE**: 1.2% vs. 0.0% **Hepatic AE**: 0.0% vs. 1.2% **AEs considered tx-related**: nausea (n=1), dyspepsia (n=1), both in DDI group. *The "slightly" higher incidence of CV AEs in the DDI group may have been related to the medical conditions for which the interacting medications were taken (6 of the 8 pts in the DDI group who had a CV AE had a h/o CV disease).	"Topical application of DSG for knee osteoarthritis was associated with only a small increase in AEs when used concomitantly with medications known to have major or moderate interactions with diclofenac…. Clinicians may cautiously consider topical DSG to treat osteoarthritis pain in the knees of patients receiving multiple medications." Limitations: • Small sample size • Analyses by age or other variables were not possible. • Dose was for one knee.

Long-term Safety Study

One long-term safety study evaluated the risks of gastrointestinal, cardiovascular or application site dermatitis adverse events in patients with versus without various risk factors for gastrointestinal, cardiovascular or renal adverse events (Table 10).

Table 10 Long-term Safety of Diclofenac Sodium Gel in Patients with Risk Factors for Adverse Events

Reference, Design, Methods, Population	Results	Authors' Conclusions Study Limitations
Peniston, et al. (2012)[57] MC long-term OLE in pts w/OAK assessing the tolerability of DSG in elderly pts and pts with risk factors for GI, CV or renal AEs. N = 583 pts who either continued DSG 1% for 9 mos after completing a 12-wk trial (N = 291) or were tx-naïve and received 12 mos of tx (N = 292). Exclusions from the tx-naïve group included pts with evidence of PUD or h/o GIB or a significant medical condition such as severe or uncontrolled renal, hepatic, hematologic, endocrine, CV or neurologic disease.	The incidences of GI, CV and application-site dermatitis (ASD) were assessed for pts < 65 y vs. pts ≥ 65 years, and pts with versus those without HTN, T2DM, cerebrovascular or cardiovascular disease (CCVD), or all three comorbidities (CMs). **Risk Subgroup** / **n** / **Any AE** / **GI AE** / **CV AE** / **ASD** Age < 65 y: 575 / 392 (68.2) / 54 (9.4) / 19 (3.3) / 50 (8.7) Age ≥ 65 y: 372 / 250 (67.2) / 25 (6.7) / 12 (3.2) / 49 (13.2) W/ HTN: 438 / 287 (65.5) / 39 (8.9) / 22 (5.0) / 36 (8.2) W/o HTN: 509 / 355 (69.7) / 40 (7.9) / 9 (1.8) / 63 (12.4) W/ T2DM: 100 / 64 (64.0) / 7 (7.0) / 8 (8.0) / 10 (10.0) W/o T2DM: 847 / 587 (68.2) / 72 (8.5) / 23 (2.7) / 89 (10.5) W/ CCVD: 97 / 60 (61.9) / 12 (12.4) / 6 (6.2) / 8 (8.2) W/o CCVD: 850 / 582 (68.5) / 67 (7.9) / 25 (2.9) / 91 (10.7) W/ 3 CMs: 15 / 8 (53.3) / 0 (0.0) / 2 (13.3) / 0 (0.0) W/o 3 CMs: 932 / 634 (68.0) / 79 (8.5) / 29 (3.1) / 99 (10.6) Values denote n (%)	In patients receiving DSG therapy, the incidences of GI, CV and ASD were similar between pts < 65 y (3.3% to 9.4%) and pts ≥ 65 y (3.2% to 13.2%), and between pts with and pts without HTN (5.0% to 8.9% and 1.8% to 12.4%, respectively), T2DM (7.0% to 10.0% and 2.7% to 10.5%), CCVD (6.2% to 12.4% and 2.9% to 10.7%), or all three co-morbidities (0.0% to 13.3% and 3.1% to 10.6%). Limitations: • Small sample size (n = 15) in the group with multiple co-morbidities.

Cardiovascular adverse events (AEs) occurred at similar rates in younger versus older patients but were more common in patients with hypertension, type 2 diabetes mellitus (T2DM), cerebrovascular / cardiovascular disease or all three comorbidities than patients without these comorbidities.

The largest differences in incidences were seen between the subgroups with versus without all three comorbidities, where the absolute differences for any AE, gastrointestinal AEs or application site dermatitis ranged from 8.5% to 14.7% higher in the group without multiple comorbidities, and cardiovascular AEs were 10.2 percentage points higher in the subgroup with multiple comorbidities than the subgroup without the comorbidities.

The highest incidences for the other subgroup analyses were seen for application site dermatitis stratified by age (5.5% higher in patients ≥ 65 y than patients < 65 y) and cardiovascular AEs stratified by presence of T2DM (5.3% higher in pts with the comorbidity than in those without it).

Studies Focusing on Selected Adverse Events

Upper Gastrointestinal Bleeding and Perforation

Cases of upper gastrointestinal bleeding (UGIB) were reported to occur during therapy with the European topical diclofenac gel product (VOLTAREN EMULGEL) particularly in patients with risk factors (e.g., peptic ulcer).[95] A 1995 record linkage case-control study in Scotland (N = 1103 cases; 6593 community controls and 2184 hospital controls; 51.6% men, 860 (78%) age >50 years old) that used data from 1989 to 1992 showed that there was a significant association between 45-day or ever exposure to various topical NSAIDs and hospital admissions for UGIB or perforation in unadjusted analyses; however, there was no significant association after adjusting for confounding factors (i.e., concomitant oral NSAIDs and ulcer healing drugs) (Table 11).[58]

Table 11 Topical NSAIDs and Hospitalization for UGIB or Perforation

Exposure variable	Adj OR (95% CI)
All Cases, Community Controls	
oNSAIDs 45 d	2.6 (2.1–3.2)*
tNSAIDs 45 d	1.4 (0.8–2.5)
UHDs Ever	4.2 (3.6–4.9)*
All Cases, Hospital Controls	
oNSAIDs 45 d	2.0 (1.6–2.5)*
tNSAIDs 45 d	1.1 (0.6–1.9)
UHDs Ever	1.8 (1.5–2.1)*

Source: Evans, et al. (1995)[58]
*P <0.001; UHD, Ulcer healing drug

In contrast, oral NSAIDs were shown to have an increased relative risk of 2.6 (2.1–3.2) versus community controls and an increased relative risk of 2.0 (1.6–2.5) versus hospital controls. Ulcer healing drugs were also significantly associated with hospital admissions for UGIB or perforation. The study included 3983 patients given 6624 prescriptions of diclofenac / Voltarol; however, the study did not assess the risk of gastrointestinal harms for individual topical NSAIDs.

Acute Renal Failure

In a case-control study conducted in Scotland, prescription and hospitalization data (1990–1992) from a large purpose-built, record-linkage database were analyzed to evaluate the risk of hospitalization for acute renal failure based on recent or previous exposure to topical NSAIDs, oral NSAIDs or aspirin.[59] Six community controls and two hospital controls were matched by age and sex for each case, and all cases were validated. Elderly and high-risk patients, including 76 with a history of pre-existing chronic renal failure, were included. Results are summarized in Table 12 and Table 13.

Table 12 Crude Odds Ratios for Exposure Variables

Exposure Variable	Cases (n = 207), n (%)	Community Controls (n = 1238) , n (%)	Unadjusted Odds Ratio (95% CI)	Hospital Controls (n = 411), n (%)	Unadjusted Odds Ratio (95% CI)
Topical NSAIDs					
Recent Exposure	4 (1.9)	18 (1.5)	1.33 (0.45–3.94)	14 (3.4)	0.56 (0.18–1.37)
Previous Exposure	23 (11.1)	83 (6.7)	1.76 (1.07–2.89)*	40 (9.7)	1.17 (0.68–2.04)
Oral NSAIDs					
Recent Exposure	44 (21.3)	130 (10.5)	2.24 (1.54–3.26)*	53 (12.9)	1.84 (1.16–2.91)*
Previous Exposure	92 (44.4)	425 (34.3)	1.54 (1.14–2.08)*	172 (41.8)	1.10 (0.78–1.54)
Aspirin					
Recent Exposure	21 (10.1)	78 (6.3)	1.72 (1.02–2.89)*	54 (13.1)	0.76 (0.45–1.29)
Previous Exposure	39 (18.8)	122 (9.9)	2.14 (1.43–3.19)*	84 (20.4)	0.88 (0.58–1.35)

*P ≤ 0.041. *Recent exposure* was defined as one or more prescriptions dispensed during a 90-day period prior to the index date. *Previous exposure* was defined as one or more prescriptions dispensed at any time from January 1989 to the index date.

Table 13 Adjusted Conditional Logistic Regression Analyses

Exposure Variable	Adjusted Odds Ratio (Community Controls)	Adjusted Odds Ratio (Hospital Controls)
Previous exposure, topical NSAIDs	1.33 (0.79–2.24)	1.04 (0.60–1.83)
Recent exposure, oral NSAIDs	2.20 (1.49–3.25)*	1.84 (1.15–2.93)*
Previous exposure, aspirin	2.19 (1.46–3.30)*	0.87 (0.57–1.34)

*P < 0.001

A significant association seen for previous exposure to topical NSAIDs relative to community controls (unadjusted odds ratio 1.76) was no longer observed after adjusting for the confounding effects of oral NSAIDs and aspirin. There was no significant interaction between oral NSAIDs and the presence of either chronic renal failure or other risk factors for the odds of acute renal failure relative to either community or hospital controls. The number of cases did not allow for analyses by individual agent. The authors concluded that topical NSAIDs probably carry no independent risk, whereas oral NSAIDs, and aspirin less conclusively, may be associated with more than a two-fold increase in risk of hospitalization for acute renal failure.

Appendix 3: Clinical Practice Guidelines

Table 14 Practice Guideline Recommendations for OA Ordered by Year of Publication

Guideline	Recommendation(s) Related to Place in Therapy of Topical NSAIDs
EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT) (2007).[96]	Treatment of hand OA should be individualized according to localization of OA; risk factors (age, sex, adverse mechanical factors); type of OA (nodal, erosive, traumatic); presence of inflammation; severity of structural change; level of pain, disability, and restriction of quality of life; comorbidity and co-medication (including OA at other sites); and the wishes and expectations of the patient (Level of evidence: IV). Local treatments are preferred over systemic treatments, especially for mild to moderate pain and when only a few joints are affected. **Topical NSAIDs** and capsaicin are effective and safe treatments for hand OA (Level of evidence: Ia). For pain relief, effect size (ES) = 0.77; 95% CI 0.32 to 1.22 for topical NSAIDs. Topical NSAIDs are similar to oral NSAIDs for pain (ES = –0.05; –0.27 to 0.17). For function, there was no data for topical NSAIDs at the time of this report. Topical NSAIDs are no worse than placebo in terms of GI AEs.
OARSI recommendations for the management of hip and knee **osteoarthritis**, Part II: **OARSI** evidence-based, expert consensus **guidelines (2008)**[97]	Acetaminophen (up to 4 g/day) can be an effective initial oral analgesic for treatment of mild to moderate pain in patients with knee or hip OA. ES 0.21 (0.02–0.41). In patients with symptomatic hip or knee OA, NSAIDs should be used at the lowest effective dose but their long-term use should be avoided if possible. In patients with increased GI risk, either a COX-2 selective agent or a non-selective NSAID with co-prescription of a PPI or misoprostol for gastroprotection may be considered, but NSAIDs, including both non-selective and COX-2 selective agents, should be used with caution in patients with CV risk factors. ES 0.32 (0.24–0.39) **Topical NSAIDs** (ES 0.41; 0.22–0.59) and capsaicin (ES not reported) can be effective as adjunctives and alternatives to oral analgesic/antiinflammatory agents in knee OA.
American Academy of Orthopaedic Surgeons (AAOS). Treatment of osteoarthritis of the knee (non-arthroplasty) (2009)[98] Also see the 2014 AAOS Appropriate Use Criteria on the Nonarthroplasty Treatment of Osteoarthritis of the Knee (OAK)[99]	The authors suggest patients with symptomatic OA of the knee receive one of the following analgesics for pain unless there are contraindications to this treatment: acetaminophen [not to exceed 4 g/d] or NSAIDs **(Grade B, Level II).** The authors suggest patients with symptomatic OA of the knee and increased gastrointestinal (GI) risk (Age ≥ 60 years, comorbid medical conditions, history of peptic ulcer disease, history of GI bleeding, concurrent corticosteroids, and/or concomitant use of anticoagulants) receive one of the following analgesics for pain: acetaminophen (not to exceed 4 g/d); **topical NSAIDs;** nonselective oral NSAIDs plus gastroprotective agent; or cyclooxygenase-2 inhibitors.
American Academy of Orthopaedic Surgeons (AAOS). The treatment of glenohumeral joint osteoarthritis (2010)[100]	The work group is unable to recommend for or against the use of pharmacotherapy in the initial treatment of patients with glenohumeral [shoulder] joint osteoarthritis.
OARSI recommendations for the management of hip and knee **osteoarthritis**: part III: Changes in evidence following systematic cumulative update of research published through January 2009 (2010)[101] This was an update of cumulative evidence on efficacy for selected drug therapies.	Currently available evidence suggests that APAP has no effect on function or stiffness, and the NNTs reported in trials were variable, ranging from 2 to 8 among 3 RCTs. Based on new evidence, APAP >3 g/day is associated with an increased risk of hospitalization due to perforation, peptic ulceration and bleeding (HR=1.20, 95% CI 1.03, 1.40). Oral NSAIDs are superior to APAP for pain reduction but the effect size is small (0.20, 95% CI 0.10–0.30). For **topical NSAIDs**, there was heterogeneity in effect sizes between products, and funnel plot analyses suggested publication bias and the potential for overestimation of efficacy. Results of previous studies suggesting similar efficacy and better safety with **topical NSAIDs** compared with oral NSAIDs were supported by an additional study comparing oral and topical ibuprofen; however, after 2 years, oral ibuprofen was more efficacious but more costly.

Continued

Guideline	Recommendation(s) Related to Place in Therapy of Topical NSAIDs

Effect Sizes

Intervention	Joint	LoE	Pain	Function	Stiffness	NNT (95% CI)
APAP	Both	Ia	.14 (.05–.23)	.09 (–.03–.22)	.16 (–.05–.37)	3 (2–52)
NSAIDs	Both	Ia	.29 (.22–.35)			
COX2Is	Both	Ia	.44 (.33–.55)			
T-NSAIDs	Knee	Ia	.44 (.27–.62)	.36 (.24–.480	.49 (.17–.80)	3 (2–4)
T-Capsaicin	Knee	Ia				4 (3–5)
Opioids	Any	Ia	.78 (.59–.98)	.31 (.24–.39)		

LoE, Level of evidence; NNT, Number needed to treat for symptom relief; T-, Topical.

ES cutoffs: 0.2 is considered small, 0.5 is moderate, and > 0.8 is large.

Safety

Adverse Events	NSAIDs RR / OR (95% CI)	NSAIDs Evidence	**T NSAIDs** RR / OR (95% CI)	**T NSAID** Evidence
GI perforation	5.36 (1.79–16.10)	Meta-RCTs		
/ ulcer / bleed	2.70 (2.10–3.50)	Meta-Cohort		
	3.00 (2.50–3.70)	Meta-Case-Control		
GI perf / bleed			1.45 (0.84–2.50)	Case-control
GI events			0.81 (0.43–1.56)	Meta-RCTs
GI hospitaliz'n	1.63 (1.44–1.85)	Cohort Study		
MI	1.09 (1.02–1.15)	Meta-Cohort		

American College of Rheumatology (ACR) recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee (2012)[102]

Technical Expert Panel (TEP) conditional recommendations:

Hand OA: Either **topical or oral NSAIDs**, topical capsaicin, or tramadol. Do not use opioid analgesics or intraarticular therapies.

Knee OA: For patients failing to obtain adequate pain relief with intermittent dosing of OTC acetaminophen, OTC NSAIDs, and/or OTC nutritional supplements (e.g., chondroitin sulfate, glucosamine), use acetaminophen, oral or **topical NSAIDs**, tramadol, or intraarticular corticosteroid injections. Do not use nutritional supplements (e.g., chondroitin sulfate, glucosamine) or topical capsaicin. If the patient does not have a satisfactory clinical response to full-dose acetaminophen, then use oral or **topical NSAIDs** or intraarticular corticosteroid injections. For persons age ≥75 years, the TEP strongly recommends the use of **topical rather than oral NSAIDs**.

Hip OA: Pharmacotherapeutic approach is similar to that for the patient with knee OA except that no recommendations are made for intraarticular hyaluronates, duloxetine, or topical NSAIDs.

American Academy of Orthopaedic Surgeons (AAOS) Appropriate Use Criteria (AUC) on the Non-Arthroplasty Treatment of Osteoarthritis of the Knee (OAK) (2013)[103]

NSAIDs, oral or topical, are "appropriate" non-arthroplasty treatments for OAK.

Panel members voted NSAIDs as "appropriate" in 94% of 576 clinical scenarios and as "may be appropriate" in 6% of the scenarios. All of the scenarios for which NSAIDs were voted as "may be appropriate" involved elderly patients.

"Appropriate" meant treatment was generally acceptable and a reasonable approach for the indication and likely to improve the patient's health outcomes or survival. "May be appropriate" denoted that treatment was uncertain for the indication provided; treatment *may* be acceptable and *may* be a reasonable approach for the indication, but with uncertainty implying that more research and/or patient information was needed to further classify the indication.

Only 1 of 23 NSAID trials involved diclofenac.

OARSI guidelines for the non-surgical management of knee osteoarthritis (2014)[104]

Topical NSAIDs are listed as recommended treatment alternatives for patients who have knee-only OA with or without co-morbidities (i.e., diabetes; hypertension; cardiovascular disease; renal failure; gastrointestinal (GI) bleeding; depression; or physical impairment limiting activity, including obesity). The appropriateness of topical NSAIDs for multi-joint OA with or without comorbidities was rated as uncertain.

Continued

<table>
<tr><th>Guideline</th><th>Recommendation(s) Related to Place in Therapy of Topical NSAIDs</th></tr>
<tr><td></td><td>Recommended Treatments Appropriate for OA Clinical Sub-Phenotypes
<table>
<tr><th>Knee-only OA Without Comorbidities</th><th>Knee-only OA With Comorbidities</th><th>Multi-joint OA Without Comorbidities</th><th>Multi-joint OA With Comorbidities</th></tr>
<tr><td>Biomechanical interventions
Intraarticular (IA) Corticosteroids
Topical NSAIDs
Walking Cane
Oral Selective NSAIDs
Capsaicin
Oral Nonselective NSAIDs
Duloxetine
APAP</td><td>Biomechanical interventions
Walking cane
IA Corticosteroids
Topical NSAIDs</td><td>Oral Selective NSAIDs
IA Corticosteroids
Oral Nonselective NSAIDs
Duloxetine
Biomechanical interventions
APAP</td><td>Balneotherapy
Biomechanical interventions
IA Corticosteroids
Oral Selective NSAIDs
Duloxetine</td></tr>
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<tr><td>National Collaborating Centre for Chronic Conditions. Osteoarthritis: Care and Management. London (UK): National Institute for Health and Clinical Excellence (NICE) (2014)[70]</td><td>For knee and hand osteoarthritis, consider APAP and/or topical NSAIDs before oral NSAIDs / cyclooxygenase-2 (COX 2) inhibitors or opioids. [Based on high quality evidence from meta-analyses and RCTs]
If acetaminophen or topical NSAIDs are insufficient for pain relief, then consider adding opioid analgesics [based on high quality evidence from meta-analyses] or substituting with (or in addition to paracetamol) an oral NSAID or COX 2 inhibitor. [Based on high quality evidence from large randomized controlled trials, supplemented by meta-analysis and health economic modelling of cost effectiveness]
Consider topical capsaicin as an adjunct to core treatment. [Based on moderate quality evidence from small RCTs]
Rubefacients are not recommended for the treatment of osteoarthritis [based on moderate quality evidence from small RCTs].</td></tr>
<tr><td>VA/DoD Clinical Practice Guideline on the Non-Surgical Management of Hip and Knee osteoarthritis (OA) (2014)[105]</td><td>In patients with no contraindications to pharmacologic therapy, clinicians should consider APAP or oral NSAIDs as first line treatment.[B]
In patients requiring treatment with oral NSAIDs and who are at high risk for serious adverse upper GI events, clinicians should consider the addition of a proton-pump inhibitor (PPI) or misoprostol. [A]
Use topical NSAID therapy as an alternative to oral NSAIDs for knee OA.</td></tr>
<tr><td>UpToDate, Initial Pharmacotherapy of Osteoarthritis (2015)</td><td>Initial therapy suggested by clinical situation:
• Noninflammatory OA: Acetaminophen
• Inadequate response to acetaminophen, inflammatory OA or severe pain: NSAIDs, up to three agents if there is an inadequate response to previous NSAID.
• Cannot tolerate, had inadequate response or have contraindications to oral agents, or who may be at increased risk of adverse effects with the use of oral NSAIDs, such as older adults (e.g., patients 75 and older), or desire to avoid or delay injections: Topical NSAIDs or capsaicin; intraarticular glucocorticoids (if few joints involved and symptoms are severe).
– Topical NSAIDs are also used as an adjunct to other therapies.
– In patients who poorly tolerate oral NSAIDs, topical NSAIDs are preferred over opioids, capsaicin, or continued trials of multiple different oral NSAIDs because of the greater safety and better tolerance of the topical agent.
– In patients who cannot take oral NSAIDs, topical NSAIDs are preferred over opioids.</td></tr>
</table>

Table 15 Guidelines for Pain Therapy in Older Persons

Guideline	Recommendation(s) Related to Place in Therapy of Topical NSAIDs
American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons (2009)[106]	All patients with other localized nonneuropathic persistent pain may be candidates for **topical NSAIDs** (moderate quality of evidence, weak recommendation).
British Geriatrics Society and British Pain Society Guidance on the Management of Pain in Older People (2013)[107]	**Topical NSAIDs** may provide an alternative to oral NSAIDs, particularly if pain is localized.

Table 16 Guidelines Covering Acute Pain Therapy for Minor Musculoskeletal Injuries

Guideline	Recommendation(s) Related to Place in Therapy of Topical NSAIDs
American College of Occupational and Environmental Medicine (ACOEM) occupational medicine practice guidelines on ankle and foot disorders (2011)[74]	*Achilles Tendinopathy*: Recommended treatments include acetaminophen (I), NSAIDs (for acute Achilles tendinopathy pain (C), subacute or chronic Achilles tendinopathy pain or postoperative pain or inflammation (I), **topical NSAIDs** (for acute or subacute Achilles tendinosis (C) or chronic Achilles tendinosis (I). *Plantar Heel / "Plantar Fasciitis"*: Recommended treatments include acetaminophen (I), NSAIDs (I), **topical NSAIDs** for acute, subacute or chronic plantar fascial pain syndromes (I). *Ankle Sprain*: Recommended treatments include acetaminophen (B), NSAIDs for acute ankle sprain (A), NSAIDs for subacute, chronic or postoperative ankle sprain (I), **topical NSAIDs** for acute ankle sprain (B) Strength of Evidence Ratings: A = Strong evidence base (≥ 2 high-quality studies) B = Moderate evidence base (≥ 1 high-quality study or multiple relevant lower-quality studies) C = Limited evidence base (≥ 1 study of intermediate quality) I = Insufficient evidence (evidence is insufficient or irreconcilable)

Table 17 Cardiology Guidelines Addressing Use of NSAIDs

Guideline	Recommendation(s) Related to Place in Therapy of Topical NSAIDs
American College of Cardiology (ACC) / American Heart Association (AHA) guideline on management of patients with heart failure (2013)[75]	Heart failure with reduced ejection fraction: Avoid or withdraw NSAIDs whenever possible.
ACC/AHA guideline on management of patients with ST-elevation myocardial infarction (2013)[77]	NSAIDs are contraindicated, should not be initiated in the acute phase and should be discontinued in patients already taking them before hospitalization.
ACC/AHA guideline on management of patients with non-ST-elevation acute coronary syndrome (2014)[76]	NSAIDs (except aspirin) should not be initiated and should be discontinued during hospitalization for NSTE-ACS (increased risk of MACE). Before hospital discharge, patients requiring treatment for chronic musculoskeletal discomfort should use a stepped approach: acetaminophen, nonacetylated salicylates, tramadol, nonselective NSAIDs (such as naproxen), then NSAIDs with increasing degrees of relative COX-2 selectivity. In all cases, use of the lowest effective doses for the shortest possible time is encouraged.

Table 18 Gastroenterology Guidelines Addressing Use of NSAIDs

Guideline	Recommendation(s) Related to Place in Therapy of Topical NSAIDs
NICE guidance on management of acute upper gastrointestinal bleeding (2012)[78]	Continue low-dose aspirin for secondary prevention of vascular events once hemostasis is achieved. Stop other NSAIDs during the acute phase of bleeding.
Society of Danish Society for Gastroenterology and Hepatology guideline on management of bleeding gastroduodenal ulcers (2012)[79]	Aspirin can be paused for 24 h until bleeding has stopped and patient is stabilized. Hold NSAIDs in the presence of ulcer bleeding. Low-dose aspirin can be resumed after 24 h if there is no sign of bleeding in progress and high-dose intravenous PPI is given. Discontinue unnecessary NSAID intake. For aftercare of patients with a need to continue aspirin or NSAID therapy, give prophylactic PPI therapy at standard doses.
American College of Gastroenterology (ACG) practice guidelines on management of patients with ulcer bleeding (2012)[80]	For long-term prevention of recurrent bleeding ulcers associated with *Helicobacter pylori*: add antisecretory therapy if NSAIDs are required. For NSAID-associated bleeding ulcers, do not resume NSAIDs if possible. If NSAID must be restarted, use a COX-2–selective NSAID at lowest effective dose plus daily PPI.
ACG guideline on prevention of NSAID-relate ulcer complications (2009)[108]	Risk categories for NSAID-related gastrointestinal complications High Risk: • History of complicated peptic ulcer disease • Multiple (>2) risk factors Moderate Risk: • 1 to 2 risk factors Low Risk: • No risk factors **Risk Factors**: • Age over 65 years • High-dose nsaid therapy • History of uncomplicated ulcer • Concurrent use of aspirin (including low doses), glucocorticoids or anticoagulants.

Table 19 Kidney Guidelines Addressing Use of NSAIDs

Guideline	Recommendation(s) Related to Place in Therapy of Topical NSAIDs
VA/DoD Clinical Practice Guideline on Chronic Kidney Disease (2014)[109]	In patients with CKD, the benefits of using NSAIDs should be carefully weighed against the possible adverse effects on kidney function. The appropriate threshold for the use of NSAIDs has not been established. Topical NSAIDs such as diclofenac are generally considered to be safe in patients with mild CKD but should be used with caution in patients with advanced CKD.
University of Michigan Health System, Management of Chronic Kidney Disease (2014)[81]	Avoid nephrotoxic medications to prevent worsening renal function. Definition of CKD: Kidney damage for ≥3 months, defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR)
Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guideline for the evaluation and management of chronic kidney disease (2013)[82]	The Work Group recommends temporary discontinuation of potentially nephrotoxic and renally excreted drugs in people with a GFR <60 ml/min/1.73 m^2 (GFR categories G3a–G5) who have serious intercurrent illness that increases the risk of acute kidney injury. These drugs include NSAIDs. Definition of CKD: Abnormalities of kidney structure or function, present for >3 months, with implications for health.

Appendix 4: Postmarketing Safety Surveillance Reports

Hepatic Effects

All NSAIDs have similar warnings about hepatic adverse effects. On December 4th, 2009, the FDA issued a safety alert informing health care professionals about the addition of new warnings and precautions to the Hepatic Effects section of the prescribing information for **diclofenac gel**. The safety alert warned that any products containing diclofenac sodium, including **diclofenac gel**, may result in liver dysfunction, severe hepatic reactions, liver transplantation, or death. Based on reports with oral diclofenac, severe hepatic reactions can occur without a prodrome and at any time during therapy. Increases in hepatic transaminases was more common in patients with osteoarthritis than in those with rheumatoid arthritis. At the time of preparation of this review, only diclofenac topical solution had prescribing information dated after the FDA safety alert (01/2010). Based on the prescribing information for diclofenac topical solution 1.5%, providers should measure transaminases (ALT and AST) within 4 to 8 weeks of initiating diclofenac and periodically in patients receiving long-term

therapy with diclofenac. Optimum intervals for transaminase tests are unknown. Providers should educate patients about the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and flu-like symptoms) and advise them to stop diclofenac therapy if they occur. If liver transaminase levels remain increased or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc.), providers should discontinue diclofenac immediately. The lowest effective dose should be used for the shortest duration possible. Caution should be used when diclofenac is prescribed with other hepatotoxic drugs, such as acetaminophen, certain antibiotics, and antiepileptics. Providers should caution patients to avoid taking unprescribed acetaminophen during diclofenac therapy.

Gastrointestinal Hemorrhage

A published report described four cases of upper gastrointestinal hemorrhage associated with the topical application of **diclofenac gel**. The 4 patients (3 males, 1 female; 24 to 86 years of age) were participants in a prospective study of primary acute upper gastrointestinal hemorrhage involving a total of 110 patients. The 4 patients had applied diclofenac gel several times daily for durations ranging from 3 days to 6 weeks preceding the onset of bleeding, with 3 patients using diclofenac gel for at least 2 weeks.[95] In two cases, hemorrhage was massive, requiring blood transfusions, and diclofenac gel had been given for backache, which in retrospect, was attributable to a peptic ulcer. In one patient, a urease test was negative for *H. pylori* (as a cause of peptic ulceration), suggesting that prolonged use of diclofenac gel was a causal factor of duodenal ulceration. The authors concluded that systemic complications can be anticipated with diclofenac gel because it is partially systemically absorbed and caution should be used with this agent in patients with a history of peptic ulcer disease. (These reports contradict the findings of a 1995 record linkage case-control study. See Upper Gastrointestinal Bleeding and Perforation, page 28.)

Hearing Loss

A systematic review / meta-analysis of 23 studies (92,532 participants) that evaluated whether NSAID use was associated with sensorineural hearing loss showed mixed results.[110] Hearing loss as a patient-reported adverse reaction was associated with NSAID use but hearing loss was not confirmed by a study that used audiometric testing. None of the studies involved topical NSAIDs.

Appendix 5: Pharmacokinetic Considerations

See Product Information for complete information on the pharmacokinetic properties of the topical diclofenac products.

Absorption and half-life parameters for the three topical analgesic diclofenac products are shown in Table 20. Making comparisons across products is difficult because of the differences in study methodologies and lack of studies directly comparing the formulations, with the exception of the 1.5% and 2% solutions, for which three comparative studies were done.[111] (Study 1 results are reported in the prescribing information and summarized in Table 20.) When these products were applied in doses of 77.2 mg/d/knee and 80 mg/d/knee, respectively, for 7.5 days, the less concentrated 1.5% solution had a lower extent of absorption than the 2% solution at steady state on day 8 (mean AUC 142 ng•h/ml versus 205 ng•h/ml; Table 20).

Table 20 Selected Pharmacokinetic Characteristics of Topical Analgesic Diclofenac Products

	Patch 1.3%		Gel 1%		Solution 1.5%		Solution 2%
Parameter	1 patch single dose	1 patch b.i.d. x 4 d	4 x 4 g (160 mg) / d to one knee x 7 d	4 x 12 g (480 mg) / d to 2 knees and 2 hands x 7 d	80 drops 4 times (total, 154 mg) daily for 7 days	19.3 mg q6h to each knee (154 mg/d) x 7.5 d[§]	40 mg q12h. to each knee (160 mg / d) x 7.5 d[§]
Absorption							
$AUC_{0–12}$, mean ± SD, ng•h/ml					745 ± 375	142 ± 92	205 ± 111
$AUC_{0–24}$, mean ± SD, ng•h/ml			233 ± 128	807 ± 478			
$AUC_{0–24}$, mean % of oral (95% CL), ng•h/ml		< 1%*	5.8[†] (5, 6.7)	19.7 (17, 22.8)	—	—	—
Cmax-plasma, mean ± SD, ng/ml (range)	(0.7–6)		15 ± 17.3	54 ± 32	19 ± 9	17 ± 11	25 ± 13
Cmax-plasma,		< 1%*	0.6	2.2	—	—	—

Parameter	Patch 1.3%		Gel 1%		Solution 1.5%		Solution 2%
	1 patch single dose	1 patch b.i.d. x 4 d	4 x 4 g (160 mg) / d to one knee x 7 d	4 x 12 g (480 mg) / d to 2 knees and 2 hands x 7 d	80 drops 4 times (total, 154 mg) daily for 7 days	19.3 mg q6h to each knee (154 mg/d) x 7.5 d§	40 mg q12h. to each knee (160 mg / d) x 7.5 d§
mean, % of oral (95% CL)			(0.5, 0.7)	(1.9, 2.6)			
Tmax-plasma, mean ± SD, h	10–20		—	—	4.0 ± 6.5 (—)		
Tmax-plasma, median, h			14	10	—		
Tmax-plasma, range, h			0–24	0–24	—		
Elimination							
Plasma Half-life, h	12		—	—	79.0 ± 38.1		

AUC, Area Under the Curve (mean systemic exposure). † As a percentage of AUC with diclofenac 50 mg p.o. t.i.d. ‡ As a percentage of AUC with a single dose of diclofenac 150 mg p.o. * As a percentage of AUC with a single dose of diclofenac 50 mg p.o. § Study 1 of reference 111.

Absorption and Distribution

The systemic absorption of diclofenac from topically applied formulations is many times lower than that for oral diclofenac. A single dose of diclofenac sodium 50 mg tablet produces a mean AUC_{0-inf} of 6300 ng•h/ml and mean Cmax of 1500 to 1600 ng/ml,[112] whereas topical formulations produce AUC_{0-12} values ranging from 142 to 807 ng•h/ml and Cmax values of up to 54 ng/ml (Table 20). In general, absorption of topically applied NSAIDs concentrate in dermis, muscle, synovium and joint cartilage, whereas plasma drug concentrations stay below 10% of those achieved after oral administration.[113] Specific information on the absorption and distribution characteristics of each topical formulation follows.

Diclofenac Epolamine Patches 1.3%

Each 10-cm x 14-cm diclofenac patch contains 180 mg of diclofenac epolamine in an adhesive material in a concentration of 1.3% (13 mg per gram of adhesive). Diclofenac patch is described as a *topical* as opposed to transdermal patch, meaning that drug is absorbed into the skin locally and has an effect on adjacent tissues. Pharmacokinetic data suggest that drug penetrates into affected joints (e.g., synovial fluid) and injured tissue (e.g., muscle) with little systemic absorption, [114] and the data support formation of a local tissue reservoir of drug at the application site.[115] Early studies showed that only 5% (9 mg) of drug is released from the patch (N = 20), and synovial concentrations are 35.9% lower than those in plasma (N = 8).[117]

Diclofenac AUC is about 40 ng·hr/ml after one application of diclofenac patch, whereas AUC is about 4500 ng·hr/ml after 150 mg of diclofenac orally (the recommended dose for acute pain).[116] Exposure (AUC) and Cmax after 4 days of diclofenac patch application are less than 1% of those after a single 50-mg oral diclofenac sodium tablet.[117] According to the diclofenac patch dossier, peak diclofenac plasma concentrations in patients administered a single application of diclofenac patch were ~1 ng/mL at all time points.[114] In patients administered oral diclofenac, peak plasma concentrations three hours after administration were ~400ng/mL.[117] Steady-state plasma concentrations range from 1.3 to 8.8 ng/ml following twice daily application of the patch for 5 days.

In healthy volunteers, moderate exercise resulted in no clinically relevant changes in systemic diclofenac absorption as compared with use of the patch at rest.

According to the Alpharma AMCP dossier, topical administration avoids first-pass metabolism.[114] The controlled release of diclofenac is sustained for 12 hours.

Diclofenac Gel 1%

Mean systemic exposure (AUC) with recommended dose of diclofenac 1% gel is 6% of that with oral diclofenac treatment (50 mg 3 times a day). The average peak plasma concentration is 42–151 times lower and the average systemic exposure is 5- to 17-fold lower than with oral diclofenac.[118,119] However, the results of a small placebo-controlled pharmacokinetic study in 10 patients with bilateral knee effusions suggested that distribution of the topically applied drug is predominantly via the blood, and a direct transport of drug into the knee joint was minimal.[120]

Topically applied diclofenac is absorbed to a depth of 3–4 mm, making it suitable for treatment of osteoarthritis involving the hands and knees but not the hip.[121]

No clinically relevant differences of systemic absorption and of tolerability were found between applications of diclofenac gel with and under moderate heat (application of a heat patch for 15 minutes prior to gel application) and moderate exercise (first gel application followed by a 20-minute treadmill exercise) conditions. However, concurrent use of diclofenac gel and heat is not recommended because the pharmacokinetics were not tested when heat was applied after gel application.

Diclofenac Topical Solution 1.5% (Drops)

Systemic exposure (AUC) to diclofenac following application of topical solution (4 times daily for 1 week) was about one third of the diclofenac exposure from application of diclofenac topical gel 3% (SOLARAZE; twice daily for 4 weeks).

In Study 2 of the three pharmacokinetic studies for the 2% solution, the comparators were the 1.5% solution and oral diclofenac (150 mg/d).[111] The $AUC_{0–24}$ for the 1.5% solution was 8% of that reported for oral diclofenac (354 and 4426 ng·h/ml, respectively).

DMSO improves the absorption of diclofenac when applied in multi-dose regimens. There is minimal absorption of diclofenac with single-dose, "as needed" applications.[122]

Diclofenac Topical Solution 2% (Metered Dose Pump, MDP)

This product is a more concentrated and more viscous formulation of diclofenac solution 1.5%. The pharmacokinetic Study 1 showed that the $AUC_{0–12}$ and Cmax values of the 2% viscous solution were 49% and 46% higher than those for the 1.5% solution, respectively. The FDA performed confidential, indirect evaluations of the systemic exposure to diclofenac using data from the 1.5% solution and two unverifiable pharmacokinetic studies (which were disallowed in the NDA submission) comparing the 2% viscous solution, 1.5% solution and oral diclofenac tablet (Study 2) and the 2% viscous solution versus 1.5% solution (Study 3). The FDA concluded that the AUC and Cmax values for the 2% viscous solution were "much lower" than those for oral diclofenac tablet. In Study 2, the $AUC_{0–24}$ for the 2% solution was 7% (316 ng·h/ml) of that for oral diclofenac.[111]

Appendix 6: GRADEing the Evidence

Quality of Evidence	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomesbecause of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.

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